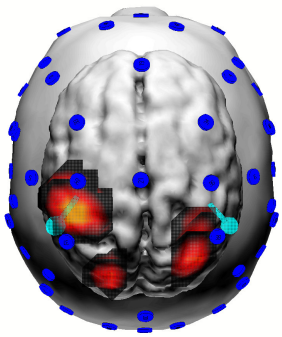
Functional brain mapping of development and familial risk for dyslexia in kindergarten children



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To my godson Nicola Maurer

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Summary

Learning to read and its disturbance, dyslexia, are important issues in a society relying on exchange of written information. However, little is known about the plastic changes in the brain induced by learning to read. This holds for both, normal or disturbed reading development. Dyslexia is a common reading disorder occurring in about 5-10 % of all school children and running predominantly in families. Dyslexia is characterised by a phonological processing deficit, possibly due to a deficit in more general auditory processing. Markers of these deficits might help concerned families to seek early training or provide relief.

This thesis is part of a larger longitudinal study investigating children with and without familial risk before and after learning to read. It focuses on plastic changes induced by learning to read, on developmental differences in automatic auditory processing, and on risk group differences in automatic auditory processing. Developmental and reading induced changes were investigated comparing kindergarten children and adults, risk group differences were investigated comparing kindergarten children with and without familial risk for dyslexia.

Functional brain mapping was applied using 43-channel event-related potential (ERP) recording. This ERP mapping approach resolves the brain activity in split-second time range, and allows topographic analyses. In addition distributed source models can estimate the active generators in the brain with reasonable accuracy of a few centimeters.

In a visual word and form repetition detection task in study one skilled adult readers showed a fast and specialised visual processing step for words (within 0.2 s, N200), which was distinct from symbol processing. Source estimation with a realistic head model located this word-specific activation among other bilateral extrastriate areas predominantly in the left fusiform gyrus. Illiterate kindergarten children lacked a reliable, fast and specialised visual processing step for words. This finding is consistent with the hypothesis, that the fast and specialised word N200 is the result of

plastic changes in the brain induced by learning to read. It is also corroborated by the behavioural results, where children missed word and symbol targets equally often, and where adults missed far fewer words than symbols. In addition, the neurophysiological results indicated a visual precursor stage of learning to read in kindergarten children occurring about half a second after stimulus presentation. This finding was not expected and might be due to visual familiarity with letters gained before the actual training.

In study two a positive mismatch response (MMR) was detected in kindergarten children, which replaced the expected mismatch negativity (MMN) and which was not present in adults. This is a new finding and its inconsistencies with previous results might be explained with the short deviance and intervals used. The occurrence of a positive MMR is relevant for developmental MMN research and clinical MMN application in children, because it may disturbs MMN results and their interpretations. In addition, with this positive MMR a new ERP component has been detected, which bears a potential of its own to investigate auditory processing deficits, although this remains to be evaluated in the future.

In study three kindergarten children at familial risk for dyslexia had an altered late MMN to frequency and phoneme deviance. These results are important, since they indicate in addition to a phonological processing deficit in dyslexia, also a more basic auditory processing deficit, and thus add more information to a field with inconsistent results. Furthermore, these group differences may are trait markers of a familial risk for dyslexia, or they might even serve as predictors of dyslexia at the kindergarten level, allowing early training and prevention of dyslexia at least in families with a genetic risk.

Zusammenfassung

Lesenlernen und seine Störung, Dyslexie, sind wichtige Themen in einer Gesellschaft, die stark auf den Austausch schriftlicher Information baut. Man weiss jedoch erst wenig über die plastischen Vorgänge im Gehirn, die das Lesenlernen begleiten. Dies gilt sowohl für die normale wie auch die gestörte Entwicklung des Lesens. Dyslexie ist eine Beeinträchtigung des Lesens, die bei etwa 5-10 % aller Schulkinder auftritt und in den gleichen Familien gehäuft vorkommt. Sie ist durch ein Defizit in der phonologischen Verarbeitung gekennzeichnet, das vermutlich auf ein Verarbeitungsdefizit von noch grundlegenderen auditorischen Merkmalen zurückgeht. Marker von diesen Defiziten könnten betroffenen Familien helfen, indem sie frühes Training ermöglichen oder durch Entwarnung beruhigen.

Diese Dissertation ist Teil einer umfassenderen Longitudinalstudie, in der Kinder mit und ohne familiärem Dyslexie-Risiko vor und nach dem Lesenlernen untersucht werden. Die Dissertation fokussiert auf Plastizität des Lesenlernens sowie Entwicklungs- und Risikogruppenunterschiede in der automatischen auditorischen Verarbeitung. Entwicklung und Lesenlernen werden durch Querschnittsvergleiche zwischen Kindergartenkindern und Erwachsenen, Risikogruppenunterschiede durch Vergleiche zwischen Kindergartenkindern mit und ohne familiäres Dyslexie-Risiko untersucht.

Funktionelles Brain Mapping wurde angewendet, indem ereignisbezogene Potentiale (ERP) mit 43 Kanälen aufgezeichnet wurden. Dieser ERP Mapping Ansatz misst die Gehirntätigkeit in Bruchteilen von Sekunden und ermöglicht topographische Analysen. Zusätzlich können die Generatoren mit einer Genauigkeit von wenigen Zentimetern einigermassen vernünftig modelliert werden.

In einer Aufgabe zur Erkennung von sich wiederholenden visuellen Reizen wiesen erwachsene, geübte Leser einen visuellen Verarbeitungsschritt auf, der für Wörter spezialisiert war und sehr schnell auftrat (nach 0.2 s, N200). Quellenlokalisation mit einem realistischen Kopfmodell lokalisierte diese wortspezifische Aktivierung neben anderen bilateralen extrastriären Arealen vor allem im linken fusiformen Gyrus. Die

Kindergartenkinder, die noch nicht lesen konnten, wiesen diese schnelle und spezialisierte visuelle Wortverarbeitung noch nicht auf. Dieser Befund ist im Einklang mit der Hypothese, dass diese spezialisierte Wort-N200 das Ergebnis plastischer Veränderungen ist, die beim Lesenlernen geschehen. Die Verhaltensdaten bestätigten, dass die Kinder noch nicht lesen konnten, da sie im Gegensatz zu den Erwachsenen, Wörterwiederholungen nicht besser erkannten als Symbolwiederholungen. Zusätzlich deuteten die neurophysiologischen Daten auf ein visuelles Vorstadium des Lesenlernens bei den Kindergartenkindern hin, das nach etwa einer halben Sekunde auftrat. Dieses Ergebnis war nicht vermutet worden, ist aber wohl eine Folge der visuellen Vertrautheit mit Buchstaben, die schon vor dem Training angeeignet wird.

In der zweiten Studie wurde bei den Kindergartenkindern eine frontal positive Mismatch Response (MMR) gefunden, die anstelle der erwarteten Mismatch Negativität (MMN) auftrat und bei den Erwachsenen nicht zu finden war. Dieser neue Befund widerspricht der Lehrmeinung einer in der Entwicklung stabilen MMN und ist möglicherweise eine Folge der Verwendung von geringen Abweichungen und kurzen Intervallen. Die positive MMR ist für MMN Entwicklungsforschung und klinische Anwendungen von grosser Bedeutung, da sie die MMN Ergebnisse und deren Interpretation stören kann. Sie ist aber auch eine eigenständige, neu entdeckte ERP Komponente, die ein eigenes Potential für Anwendungen in Forschung und Klinik hat, was aber in Zukunft erst noch geprüft werden muss.

In der dritten Studie zeigten sich bei Kindergartenkindern mit einem familiären Dyslexierisiko Unterschiede in der späten MMN bei Tonhöhen- und Phonemabweichungen. Diese Ergebnisse bestärken die Annahme eines phonologischen Defizits bei einer Dyslexie, aber auch das Vorliegen eines Defizit in grundlegender auditorischen Verarbeitung, wozu bisher in der Literatur unterschiedliche Befunde vorlagen. Diese Gruppenunterschiede sind vielleicht nur ein Merkmal eines Dyslexie-Risikos, vielleicht eignen sie sich aber auch als Prädiktoren einer späteren Dyslexie bei solchen Risikogruppen. Dadurch könnte schon im Kindergarten präventives Training stattfinden oder aber besorgte Familien könnten entwarnt werden.

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Abbreviations

3D	3-dimensional
EEG	electroencephalogram
ERP	event related potential
fMRI	functional magnetic resonance imaging
GFP	global field power
ISI	interstimulus interval
LORETA	low resolution electromagnetic tomography
MANOVA	multivariate analysis of variance
MEG	magentoencephalogram
MMN	mismatch negativity
MMR	mismatch response
PET	positron emission tomography
SD	standard deviation
SOA	stimulus onset asynchrony
TANOVA	topographic analysis of variance
VWF	visual word form (area)

1. Introduction

In a society relying much on the exchange of information, learning to read is a most important achievement a child makes during its development. The importance of reading ability in the public opinion was recently demonstrated by the wide media echo, when the PISA study (Programme for International Student Assessment) reported only average reading abilities in Switzerland at age 14, partly due to late school enrolment, low educational interest in families and high rate of foreign language backgrounds (Moser, 2001). Thus, to provide a good education in reading ability, examination of the factors involved are crucial, be it at the social or educational level or be it at the individual level investigating brain processes of learning to read.

Printed words become linked to sound and meaning for the first time when children learn to read them. During this process new brain areas become specialised and different areas get functionally connected to build a neural network for word processing. These permanent changes in the brain are called plasticity induced by learning to read.

Compared to most other countries, in Switzerland the formal reading training starts relatively late at age 7 when the children enter school. Before that most children visit kindergarten, where they are not allowed to be taught to read. As a consequence Swiss children learn to read relatively late, and at an age when phonological skills are already well developed. Because phonological skills are a prerequisite for the phoneme-grapheme linkage, learning to read is supposed to happen fast in these children. Thus this situation offers an excellent opportunity to investigate the plastic changes during learning to read in a short time period, using functional brain mapping technique during psychological tests in children before and after learning to read. However, the plasticity of brain functions involved in learning to read can also be identified comparing non reading kindergarten children with skilled adult readers. In addition to these changes in brain functions specifically related to reading ability,

changes which are a consequence of general development are expected and must be controlled.

A large number of children show difficulties in learning to read despite normal educational resources, intelligence and sensory abilities. Many of these dyslexic children suffer throughout their whole school career from their reading difficulties, and are often still troubled as adults. Since dyslexia is running in families, parents with their own experience of reading difficulties sorrow for their children wishing them more ease in learning to read. Thus, early detection of dyslexia would allow to prevent reading difficulties by early training or to comfort parents, when a dyslexia could be ruled out.

The question of early detection addresses also the issue if processing deficits in preschool children at familial risk for dyslexia are confined to children actually developing a dyslexia later in school or if these deficits are present as trait markers for a familial risk in most of the children without leading to dyslexia in each child. Comparing kindergarten children at risk with controls at processing different tasks might find group differences, which may are just trait markers or could even be used for early detection of dyslexia.

1.1 Event-related potentials (ERP) in functional brain mapping

1.1.1 ERP basics

A rapidly changing electric potential difference between two electrodes can be recorded from the scalp. This was first described for humans in 1929 by Hans Berger and called electroencephalography (EEG). The potential differences on the scalp unless caused by eye movements or muscle activity are due to electric activity of the brain. Postsynaptic potentials of many neurons are summated up, and propagated passively to the scalp, if they are aligned in parallel and are synchronously active with the same polarity (Nelson and Monk, 2001).

These electric potential differences are oscillating with amplitudes of about 10-100 μV. The smaller ERPs (0.1-20 μV) are time-locked to a repeated event and were first described by Dawson (1951). By averaging many EEG epochs around a stimulus marked by a trigger, the signal-to-noise ratio of the time-locked stimulus processing in the brain can be enhanced. Traditionally, the resulting ERPs are visualised as waveforms at each electrode. The ERPs are ususally divided into several components, which are termed by their polarity as P ("positive") or N ("negative") and the time (e.g. P100: positive component after about 100 ms) or order (e.g. P1: positive component number one) of their occurence after stimulus presentation. The components can be described with peak amplitude and peak latency. However, when using more than one recording electrode, it might happen, that at different channels components occur at different latencies or at the same latency with inverted polarity. Furthermore, when using different recording references e.g. nose or ear lobes, the waveforms can alter dramatically. To deal with such problems topographic approaches in ERP analysis were developed.

1.1.2 Topographic ERP analysis

To record the electric field or topography of an ERP a large number of electrodes are used an referred to a common reference. As Lehmann (1987) pointed out, the voltages obtained at one moment in time from a set of scalp electrodes can most simply be viewed as a landscape-like map. Potential values between actually measured values at electrodes can be interpolated and identical values connected by isopotential contour lines. The shape of this map is the same when different points are used as recording references, but when another reference point is chosen, the values at all electrodes are shifted to the same extent in positive or negative direction, because the new reference becomes the zero point. To deal with this relativity of the field and because there is no point available which has really zero potential, the average reference can be used, which means that the average potential values of all

recorded electrodes are taken as zero point (Offner, 1950; Lehmann and Skrandies, 1980; see Appendix). As a consequence each ERP component consists of a positive and a negative pole (or even more than one pole), which is physiologically meaningful because of the electric dipol character of the neuronal sources. The sources of a given topography are not supposed to lie under the positive or negative pole of the field, but under the most closely spaced field gradients, which may be exactly between the poles in the case of a tangential source (Lehmann, 1987).

The hilliness of the landscape or map strength can be indexed by the Global Field Power (GFP, see Appendix), which is computed as the root mean square (RMS) of the voltage values at the electrodes recomputed against average reference (Lehmann and Skrandies, 1980).

Lehmann and Skrandies (1980) showed that the topography of successive ERP maps usually remains stable over tens of milliseconds and then suddenly undergoes a transformation into a new topography stable over further tens of milliseconds. Such stable map topographies were later called microstates (Lehmann, 1991). The degree of change between two successive maps can be calculated with Global Dissimilarity (see Appendix) which is the standard deviation of the differences between two maps over all electrodes after normalisiation (GFP = SD = 1). Changes in map topography, and thus high dissimilarity values, typically coincide with troughs in the GFP curve, while during GFP peaks topography tends to remain stable (Lehmann and Skrandies, 1980). Map topography can be measured by the location of the 3-dimensional positive and negative centroids. Map centroids are computed separately for each polarity as the voltage-weighted mean of the electrode x-, y-, and z-coordinates (Brandeis et al., 1994). A statistical topographical approach to test differences between two maps (conditions or groups) is Topographical Analysis of Variance (TANOVA; Strik et al., 1998). This method generates an empirical probability distribution of the dissimilarity statistic by randomly shuffling the maps of the original data into pairs with their dissimilarities, according to a Monte-Carlo-randomisation (Manly, 1991). Comparing the actual dissimilarity between the two map conditions or groups with this probability distribution under the null hypothesis

of "no difference" the significance level can be estimated. Originally, dissimilarity was only computed between maps which were normalised. Thus, TANOVA on dissimilarity of normalised maps tests only differences in topography. However, TANOVA can also be computed on dissimilarity of raw maps, which detects also differences in map strength with otherwise identical topography.

GFP as the measure for global map strength varies with source strength, i.e. how many neurons with similar orientation and polarity are simultaneously active. In contrast, map topography changes with alteration of source location and/or orientation.

1.1.3 ERP source localisation

ERP maps do not contain direct spatial information about the location of the electrophysiologically active source in the brain. However, they contain spatial information about the electric field on the scalp, i. e. on a shell surrounding the brain. Whereas the electric field on a sphere can be non-ambiguously computed with a given source geometry (locations, strength and directions), the reverse is not possible, and leads to numerous possible source solutions. This is called the inverse problem, and can only be solved using additional restrictions.

There are mainly two different approaches which made these restrictions in different respects. Dipole modelling needs a predefined number of point sources to estimate their location (Scherg and von Cramon, 1985), but is problematic, if the number of sources are unknown or if the sources are known to be extensively distributed. Low resolution electromagnetic tomography (LORETA) computes the "smoothest" of all possible 3-dimensional current source density distributions which produce exactly the measured field (Pascual-Marqui et al., 1994, Pascual-Marqui et al., 1999). This smoothness constraint implies that neighbouring voxels must be similarly active, which is biologically meaningful, but also produces "blurred" pictures. Both, dipol source localisation and LORETA, originally use spherical head

models for computation. More realistic head models of the brain and the surrounding tissue may improve source localisation for both methods, especially for inferior located sources (Fuchs et al., 2001; Fuchs et al., 2002).

Although source estimation algorithms can reach a spatial resolution of around one centimeter, this only holds for very few simple source geometries, which must be known in advance. Other functional brain mapping methods (functional magnetic resonance imaging, fMRI; positron emission tomography, PET) usually provide spatial information more acurately, because they represent direct spatial measurements. However, whereas ERPs record electrical cortical and subcortical activity, fMRI relies on hemodynamic changes in the brain, and the relationship between these two measures still needs to be clarified (Vitacco et al., 2002).

Magnetoencephylography (MEG) records the magnetic field, orthogonal to the electric field produced by neural generators, also on the scalp, but its source localisation is less ambiguous than for ERPs. This is, because radial sources generate no measureable magnetic field outside a sphere, and because magnetic fields are not far reaching and thus can only be measured if originating from superficial sources. MEG has a time-resolution, which is comparable to ERP, and its source estimation is more accurate, but at the price of detecting only parts of the active sources.

1.2 Development

As daily experience tells us, children undergo large developmental changes growing up from childhood to adulthood. Major developmental changes have been reported also for ERP components. In visual processing tasks Grossi et al. (2001) reported longer latencies and larger amplitudes for younger children compared to older children for most ERP components studied. Particularly with complex visual tasks or stimuli, children had longer latencies (Kok and Rooijakkers, 1985; Taylor and Smith, 1995; Taylor and Keenan, 1999) and larger amplitudes (Taylor and Smith, 1995;

Taylor and Keenan, 1999), and also different topographies than adults (Kok and Rooijakkers, 1985; Taylor and Smith, 1995).

The same pattern can be observed in auditory tasks. However, developmental changes in topography and component sequence are pronounced even with simple stimuli and tasks. Latencies and amplitudes of auditory ERPs become shorter and smaller as the child grows up (Ponton et al., 2000 Sharma et al., 1997). In addition, children usually show a frontocentral P100-N250 ERP component sequence which is different from adults, which typically show a frontocentral P1-N1-P2-N2 sequence. This developmental difference is further modulated by the presentation rate of the stimuli. With a slow rate additional components emerge in children, which makes their component sequence more similar to the typical adult sequence (Ceponiené et al., 1998), whereas with a fast rate adults show an enhanced frontocentral P1 and a reduced N1, which makes their component sequence more similar to the typical sequence of children (Schröger, 1996).

1.3 Automatic auditory mismatch response

An automatic mismatch response (MMR) is elicited in the ERP by any discriminable change in some repetitive aspect of auditory stimulation, irrespective of the direction of the subjects attention, and is obtained by subtracting the ERP of a frequent standard from the ERP of a rare deviant (Näätänen et al., 2001a). In adults, this MMR usually consists of a frontocentral negative / mastoid positive "mismatch negativity" (MMN) at a latency of 100-250 ms (Näätänen et al., 1978). The main neural generators of the MMN are located bilaterally in the superior temporal plane of the auditory cortex, with some evidence for additional frontal sources (Alho, 1995; Näätänen et al., 2001a). The MMN gets smaller or even disappears as the degree of deviance is reduced (Näätänen et al., 2001a). Particularly in children, this early MMN can be followed by a late MMN peaking between 400 and 500 ms (Korpilahti et al., 1995; Korpilahti et al., 2001). The MMN is considered as an index of the auditory

sensory memory or "primitive intelligence" of the auditory system, since it seems to be generated by neural traces carrying the central sound representation (Näätänen et al., 2001a). The functional role of the late MMN and its relation to the "typical" MMN still needs to be determined.

MMN has been reported to be quite stable during development. Studies investigating school children reported similar MMNs as for adults, but with slightly longer latencies (Gomes et al., 1999; Gomes et al., 2000; Gomot et al., 2000; Shafer et al., 2000). Furthermore, younger children had longer latencies than older children (Gomes et al., 1999; Gomot et al., 2000; Shafer et al., 2000). In 5-8-year-olds the MMN latency range is about between 190 and 270 ms for frequency deviance (Cheour et al., 1997; Holopainen et al., 1997; Gomes et al., 1999; Gomot et al., 2000; Shafer et al., 2000) and between 180 and 350 ms for phoneme or word deviance (Kraus et al., 1999; Korpilahti et al., 2001; Cheour et al., 2002).

MMN has been even reported in studies with newborns and infants (e.g. Cheour-Luhtanen et al., 1995). However, some infant studies reported a positive deflection instead of a negative one using frequency (Morr et al., 2002) or phoneme deviants (Dehaene-Lambertz, 2000 Leppänen et al., 2002). Similar positive mismatch responses have not been discussed for older children, although the illustrations of some studies showed that they preceded, followed or even replaced the MMN in some conditions (Holopainen et al., 1997; Gomes et al., 1999; Gomot et al., 2000; Shafer et al., 2000; Korpilahti et al., 2001; Cheour et al., 2002).

A positive deviant-standard difference in automatic auditory processing, called P3a or novelty P3, and occurring between about 200 and 350 ms, has been also reported for adults (Courchesne et al., 1975; Squires et al., 1975; Simons et al., 2001) and children (Gumenyuk et al., 2001). However, a P3a/novelty P3 is only elicited when large or novel deviance is used, and appears to reflect involuntary capture of attention or orienting (Friedman et al., 2001).

1.4 Visual word processing

An important part in reading consists of visual processing of words. Specialised visual areas for word processing have been hypothesised long ago based on cases with selective „word blindness“ resulting from circumscribed occipital lesions (Dejerine, 1892). After processing of basic visual properties, an intermediate processing step specialised for letters or whole words is supposed to precede word analysis at a higher language level including phonology and semantics, at least in skilled readers.

Neurophysiological research has demonstrated that visual regions play an active role in the initial phase of specialised word processing. Consistent results have been obtained across a variety of neurophysiological methods and task conditions. Intracranial recordings with epileptic patients revealed negative peaks around 200 ms after letter string presentation, bilaterally in the posterior fusiform gyrus, but no activation when coloured checkerboards were presented (Allison et al., 1994).

In a similar time range (peak latencies: 150-200 ms) ERPs recorded from the scalp detected word or letter specific activation (Brandeis et al., 1995; Bentin et al., 1999; Cohen et al., 2000; Khateb et al., 2001). The word N200 is most prominent at occipito-temporal electrodes, occurs in explicit (Brandeis et al., 1995) and implicit (Bentin et al., 1999) reading tasks, and appears to correspond to visual processing only, since it was not modulated by phonological (Bentin et al., 1999) or semantic (Brandeis et al., 1995; Bentin et al., 1999; Khateb et al., 2001) manipulations. Furthermore, the N200 to words tends to be more left lateralised (Brandeis et al., 1995; Bentin et al., 1999), at least during its second part (Cohen et al., 2000).

Similar results were obtained in a MEG study during passive watching conditions. The earliest difference between word and symbol processing was found at about 150 ms. Source modelling localised this print-specific activity to the left inferior occipito-temporal cortex. Prior to that (at about 100 ms) identical activation for words and symbols was obtained (Tarkiainen et al., 1999).

Metabolic neuroimaging (PET, fMRI) studies also revealed consistent print-related activation in visual and posterior temporal regions during reading and in feature detection involving only implicit reading (Price et al., 1996). Inferior occipito-temporal regions, particularly a visual word form area (VWF) in the left posterior fusiform gyrus, are consistently activated in those subjects showing the left posterior temporal N200 ERP negativity in the same naming test (Cohen et al., 2000). In addition, left medial extrastriate and lateral extrastriate activation to word or word-related stimuli was reported by Petersen, Fox, Posner, Mintun, and Raichle (1988).

1.5 Learning to read

While learning to speak appears to be natural and to follow the mere exposure to spoken language, learning to read is a cultural invention and seems to be a much harder skill to master (Shaywitz, 1996). Abstraction of the phonemic units of speech (phonological ability) is a prerequisite in learning the letter-phoneme correspondence, but it develops quite late in childhood (Liberman et al., 1974). Thus, children usually start learning to read between about 5 and 7 years.

During learning to read visual and speech processing are supposed to become intensively connected (Shaywitz, 1996). The forming of a visual area specialised to recognize letters or whole words might play an important role in linking basic visual and higher language areas. Furthermore, the plastic changes in the visual word form area might be tuned by higher language processing as e.g. phonological processing (Cohen et al., 2002). Learning to read thus also represents an important model of late training induced brain plasticity during childhood.

However, the process of learning to read of children has hardly been investigated directly with functional brain mapping studies. In a series of early ERP studies visual word processing before and after formal reading instruction was examined. Children aged 5-6 at the pre-reading age (Licht et al., 1986; Licht et al., 1988; Licht et al., 1992) were taught four words before reading them repeatedly in a word naming test

with ERP recordings. An association between more positive right hemispheric ERP amplitudes after 350 ms, and less time needed to learn reading these new words was observed. The authors interpreted these results as a right hemispheric involvement in early reading acquisition. However, it remains unclear to which brain function the reported difference is related. No source localisation was computed and the difference occurred after the N200 component, and thus presumably after activation of the VWF area. Furthermore, no electrodes covering occipital or temporal regions were included, and the intensive reading training is difficult to relate to more natural word processing.

The same word naming task was compared with picture naming in 5-6 year olds and in adults (Kok and Rooijakkers, 1985). Contrary to the authors expectations age- and reading skill-related changes were not more pronounced for the word reading than for the picture naming test.

1.6 Dyslexia

1.6.1 Definition

Developmental dyslexia is a common learning disorder occurring in about 5-10 percent of the school children (Schulte-Körne et al., 1998; Kujala and Näätänen, 2001) and is defined as a specific disability in learning to read, which cannot be explained by young age, visual problems or low education (Dilling et al., 1993). Some authors recommend to diagnose dyslexia only when reading ability is discrepant to the general intelligence level (Schulte-Körne, 2001). But there is little evidence that IQ-discrepancy identifies distinct deficits or different treatment responses. In addition an IQ discrepancy criterion seems to be more reasonable for children with a low IQ, but it might be less meaningful for children with a high IQ: highly intelligent children would be diagnosed as dyslexic with reading abilities comparable to those of most other children.

1.6.2 Processing deficit hypotheses

Dyslexia is supposed to be characterised by a core deficit in phonological processing (Liberman et al., 1974; Shaywitz, 1996). This so-called phonological deficit hypothesis suggests that dyslexics are impaired in perception and manipulating of the phonemic units of spoken language, and thus also impaired in linking graphemes to phonemes. However, the phonological processing deficit could be caused by a more basic auditory processing deficit. Such an explanation is provided by the temporal auditory processing deficit (Tallal, 1980), which suggests that dyslexics are impaired in processing auditory information, which is temporally sensitive as e.g. formant transitions in phonemes.

In addition to deficits in auditory processing, also visual processing deficits have been postulated. The so-called magnocellular deficit hypothesis postulates a selective impairment of the visual transient system in dyslexics, leading to an impaired sensitivity for low contrast (Lovegrove et al., 1980) or coherent visual motion (Talcott et al., 2000). The motion detection system is known to be important for the direction of visual attention, eye movements, and visual search, and thus is presumably also involved in the reading process (Stein, 2001). The magnocellular deficit hypothesis may even be expanded from the visual modality to the auditory modality, and might cause the deficits in auditory temporal processing (Tallal, 1980 Stein, 2001). However, the specific role of the magnocellular pathway in reading high contrast words at fixation remains unclear.

1.6.3 Familial risk for dyslexia

Dyslexia has a substantial genetic or familial background. About 35 to 55 % of children with a dyslexic first grade relative will have reading difficulties themselves (Gallagher et al., 2000; Pennington and Lefly, 2001). Gallagher et al. (2000) reported deficits in early speech and language skills in preschool children with familial risk for dyslexia compared to control children, which suggests an overlapping between

specific language impairment diagnosed in preschool children and dyslexia diagnosed later in school. Pennington and Lefly (2001) reported mainly phonological deficits in preschool children at risk compared to controls.

1.6.4 Early prediction and prevention of dyslexia

Tests with phonological tasks have been developed to predict reading difficulties in preschool children. In Germany the "Bielefelder Screening zur Früherkennung von Lese-Rechtschreibschwierigkeiten (BISC)" can be used with preschool children ten or four months before school enrolment (Jansen et al., 1999). The BISC test consists of several subtests probing mainly phonological awareness, but also attention and memory. The result of the BISC indicates a risk (high or low probability) to develop a dyslexia. The BISC can also be applied for Swiss children, but some items must be adapted to Swiss German dialect, and there are no published norms for Switzerland available.

Children with poor phonological abilities can be trained in order to lower the risk to develop dyslexia. For German language the "Würzburger Trainings programm" has been shown to effectively improve learning to read in Kindergarten children with low phonological abilities (Schneider et al., 1998; Schneider, 2000), with the highly significant improvement lasting at least until grade 2.

1.6.5 Functional brain mapping of reading in dyslexia

Investigating sentence reading in dyslexic children with ERP brain mapping Brandeis et al. (1994) reported differences in both early sensory-visual (P100) and late cognitive-linguistic (N400) processing compared to controls. The amplitude of the left occipital P100 component was reduced in dyslexic children, but latency of the P100 microstate tended to be shorter in dyslexics. Additionally, dyslexic children had a delayed N400 to unexpected endings, and topographic differences of the N400

component for correct and incorrect sentence endings also distinguished dyslexic children and controls (Brandeis et al., 1994). In a MEG study letter-string-specific activation around 150 ms after stimulus presentation was found in the left inferior occipito-temporal cortex of controls (presumably the VWF area), but could not be detected in dyslexic adults (Helenius et al., 1999). However, in contrast to the Brandeis study, no differences were found earlier around 100 ms. Differences between dyslexics and controls were also reported in explicit and implicit reading using PET (Paulesu et al., 2001) and phonological processing using fMRI (Georgiewa et al., 1999; Temple et al., 2000; Georgiewa et al., 2002). In conclusion, as might be expected investigating the reading process itself, differences were found between dyslexics and controls and were found for phonological and semantic processing, but also for earlier predominantely visual processing.

1.6.6 Functional brain mapping of automatic auditory processing in dyslexia

In addition to differences in visual processing, group differences between dyslexics and controls were also investigated in automatic auditory processing. In dyslexic adults compared to controls MMN area was attenuated to small frequency deviance, whereas no difference was reported to duration deviance (Baldeweg et al., 1999). In contrast in another study, using similar frequency deviance neither MMN nor late MMN were attenuated in dyslexic school children, whereas the late MMN to phoneme deviance was attenuated (Schulte-Körne et al., 1998). Similarly, reduced late phoneme MMN was obtained in dyslexic adults but no differences in frequency MMN using larger deviance (Schulte-Körne et al., 2001). One study (Hugdahl et al., 1998) even reported a larger frequency MMN in dyslexic school children compared to controls using a similar deviance as Baldeweg et al. (1999) and Schulte-Körne et al. (2001). Whereas the group differences in frequency MMN are inconsistent, the results regarding group differences in late phoneme MMN are more clear, although only twice studied by the same research group (Schulte-Körne et al., 1998; Schulte-

Körne et al., 2001). The attenuated late phoneme MMN in dyslexics might be related to an attenuated mismatch response to complex tone pattern deviance in dyslexics (MMN: Kujala et al., 2000; late MMN: Schulte-Körne et al., 1999). Deviant MMN topographies in dyslexic groups have not been reported or investigated in any of these studies except for a more posterior located MMN to tone pattern deviance followed by a less right side late MMN preponderance in dyslexic adults (Kujala et al., 2000).

Differences in automatic auditory processing were not only reported between dyslexics and controls, but also between infants with and without familial risk for dyslexia. Using pseudowords as deviants and standards, infants at risk showed a larger positive mismatch response than controls, especially over the left hemisphere (Leppänen et al., 1999; Leppänen et al., 2002). This might indicate that the two brain hemispheres are differentially involved in automatic speech processing in infants at familial risk for dyslexia compared to controls.

1.7 Conclusions

Learning to read is one of the major landmarks during a child's development. However, little is known about the brain mechanisms involved in these plastic changes. To my knowledge learning to read was not investigated by functional brain mapping studies except for a series of early ERP studies using only a few channels, which did not cover the posterior temporal sites suited to capture visual word processing. In contrast to fMRI or PET studies, an ERP mapping study will be able to detect processing changes occurring in time, and gross localisation of the sources can be estimated. Furthermore, ERP mapping might be better suited for young children than fMRI, PET or MEG because it is less disturbed by head motion and less intimidating. Although learning to read can best be investigated in a longitudinal design recording the same children twice before and after learning to read, a first and faster analysis giving new insight in learning to read can also be done comparing Kindergarten children and adults. Thus an ERP mapping study seems promising in

recording kindergarten children and comparing their visual word processing with adult skilled readers.

Plastic changes of the brain induced by learning to read should be distinguished by plastic changes related to a more general development. In earlier ERP studies younger children had longer latencies and larger amplitudes than older children or adults in most components. Similar differences can be expected when comparing kindergarten children with adults using visual and auditory paradigms. Such differences should affect visual processing of all stimulus conditions and not be restricted to visual word processing alone. In addition, changes in ERP map topography are expected, as it has been also reported in some previous studies.

Dyslexics and controls show differences in automatic auditory processing. However, these results have been consistent for phoneme deviance, but not for frequency deviance. Whether dyslexia is based on a phonological speech processing deficit only, or on a more basic auditory processing deficit, is still an open question. Although a dyslexia can be diagnosed only after learning to read from about 2nd grade on, there is evidence for group differences between children at a familial risk for dyslexia and control children. Such differences in automatic phoneme processing have been reported already for infants at risk. However, it has not been investigated with older preschool children from dyslexic families with dyslexia. According to these infants studies, kindergarten children with a familial risk might show differences in automatic auditory processing compared to control children. These differences might be restricted to phoneme deviance, but might also extend to frequency deviance.

2. Implicit learning to read: neurophysiological evidence from kindergarten children [1]

2.1 Introduction

Learning to read represents a major landmark during normal child development. Visual processes become specialised for print processing and linked to language functions, which implies a plastic reorganisation of the brain.

Reading has long been known to depend on specialised visual areas interfacing between classical visual and language regions, mainly because selective „word blindness“ may result from visual lesions (Dejerine, 1892). Neurophysiological research has since demonstrated that these visual regions play an active role in the initial phase of specialised word and print processing. Consistent results have been obtained across a variety of neurophysiological methods and task conditions. The most direct evidence - even though limited to patients with intractable seizures and a small set of inferior-temporal regions tested - comes from intracranial recordings. Letter strings evoked bilateral negative peaks after 150 - 220 ms (N200) in posterior fusiform gyrus; the regions activated by letter strings and faces were nearby but did not overlap. This N200 was absent for coloured checkerboards, and preceded the more anterior temporal P400 activation reflecting lexical and semantic features (Allison et al., 1994). Intracranial data also indicates that word related activation progresses from posterior to anterior temporal structures within the first 400 ms (Fernandez et al., 2001). Mapping of scalp recorded event-related potentials (ERP) during silent sentence reading, Brandeis et al. (1995) identified a N200 microstate with left lateralised occipitotemporal activity (negative potentials and field gradients) to words. In contrast to the subsequent N400 microstates, this N200 was unaffected by semantic congruity. Increased occipitotemporal N200 activation with orthographic

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material appears to be largely automatic. This was reported by Bentin et al. (1999) using a visual feature detection test with letter- and symbol-strings involving only implicit reading. Here, the earliest orthographic – non orthographic difference in the ERP was a larger N200 component at the left hemisphere for orthographic (words, pseudowords, consonant strings) compared to non orthographic stimuli (symbols, forms). Furthermore, the authors showed that this N200 was not modulated by semantic or phonological conditions. Similar results were obtained in a MEG study during passive watching conditions. The earliest difference between word and symbol processing was found at about 150 ms. Source modelling localised this print-specific activity to the left inferior occipitotemporal cortex. Prior to that (at about 100 ms) identical activation for words and symbols was obtained (Tarkiainen et al., 1999).

ERP studies have further resolved distinct activation within the N200 time range. Cohen et al. (2000) reported that the N200 was contralateral to the presentation hemifield up to about 170 ms (N200 onset), but left lateralised after 200 ms regardless of the presentation hemifield (N200 peak). Similar results backed by tomographic source solutions were reported by Khateb et al. (2001; see also Michel et al., 2001).

Metabolic neuroimaging (PET, fMRI) studies also revealed consistent print-related activation in visual and posterior temporal regions during reading and in feature detection involving only implicit reading (Price et al., 1996). Inferior occipito-temporal regions, particularly a visual word form area (VWF) in the left posterior fusiform gyrus, are consistently activated in those subjects showing the left posterior temporal N200 ERP negativity in the same naming test (Cohen et al., 2000). In an additional fMRI study (Cohen et al., 2002), letter strings elicited more activity in the left VWF area than checkerboards; this difference was more pronounced in blocked than in randomized presentations. In addition, left medial extrastriate (real words, pseudo words, not consonant strings) and lateral extrastriate activation (but also false fonts) was reported by Petersen et al. (1988).

Developmental aspects of visual print processing have been explored in several comparisons between the ERPs of younger and older readers, but mainly using few

channels and with a focus on later components. In particular electrodes over extrastriate posterior-temporal regions were not included in any of the studies (except Taylor and Smith, 1995 and Taylor and Keenan, 1999). Taylor and Smith (1995) studied ERPs of 9 to 19 year old children to verbal (words and 3-digit numbers) and abstract figural stimuli during a recognition memory test. However, only ERP components subsequent to the N200 were examined. As in other visual tests, children had longer latencies (Kok and Rooijakkers, 1985; Taylor and Smith, 1995; Taylor and Keenan, 1999) and larger amplitudes (Taylor and Smith, 1995; Taylor and Keenan, 1999) than adults and had different topographies from adults (Kok and Rooijakkers, 1985; Taylor and Smith, 1995). Grossi et al. (2001) investigated the N200 component (N180/P200) in a visual rhyming task and reported amplitude and latency decreases between age 7 and age 23.

A direct comparison between early visual ERP components to letters and symbols was reported by Miller and Wood (1995) in 7 year old first grade children performing a simple black-white discrimination test of all visual patterns. Early letter specific ERP features included a more symmetric P120 and a larger N200 to letters than symbols. This suggests that letter-specific processing occurs even in young children within 100 to 250 ms, and even in tests requiring no reading .

Visual word processing before and after formal reading instruction was examined in a series of early ERP studies. Children aged 5-6 at the pre-reading age (Licht et al., 1986; Licht et al., 1988; Licht et al., 1992) were taught four words before reading them repeatedly in a word naming test with ERP recordings. An association between more positive right hemispheric ERP amplitudes after 350 ms, and less time needed to learn reading these new words was observed. The authors interpreted these results as a right hemispheric involvement in early reading acquisition. Although interesting, these results are probably not related to posterior-temporal word processing. No electrodes covering occipital or temporal regions were included, and the intensive reading training is difficult to relate to more natural word processing. The same word naming task was compared with picture naming in 5-6 year olds and in adults (Kok

and Rooijakkers, 1985). Contrary to the authors expectations age-related changes were not more pronounced for the word reading than for the picture naming test.

The present study investigated kindergarten children who could not yet read words using a word and symbol string (Fig. 1) repetition detection task, and compared them to adult skilled readers. We used 43-channel ERP mapping and LORETA source localisation to reveal temporal and spatial differences in children's and adults' visual word and form processing. We expected that children's word-symbol differences would be absent or, at least, would be qualitatively different from those in adults.

2.2 Methods

2.2.1 Participants

Kindergarten children without familial risk for dyslexia (n = 29, mean ±SD, years = 6.5 ±0.38, 15 males and 14 females, 4 left handed) and healthy adults (n = 13, mean ±SD, years = 26.5 ±3.30, 7 males and 6 females, 2 left handed) participated in this study. In Switzerland, children do not get training for learning to read in kindergarten, formal reading instruction starts with school at age seven. Children and their families were contacted in their kindergarten through handouts explaining that early readers and those not speaking (Swiss) German at home were excluded. All parents signed an information and consent form explaining the study and stating that the child is free to leave the study at any time and for any reasons. All kindergarten children were tested for intelligence (CFT-1; Weiss and Osterland, 1997), phonological abilities (BISC; Jansen et al., 1999), early letter and word reading abilities and visual and auditory acuity. About one and a half week (mean = 11.4, range = 4 to 55 days) later, their ERPs were recorded.

Two children with a phonological risk for dyslexia (BISC risk points > 3) and 4 children who could already read (more than 1/9 of tested words read) were excluded from statistical analysis. The remaining 23 children (11 boys, 12 girls) could name an

average of 11 upper case letters (SD=6.5), but could not read words except two children who read one word each (1 upper case word, 1 well-known trade-mark label). All children had an IQ above 85 points (mean ±SD=107.6 ±14.5). All participants had normal or corrected to normal vision and hearing as tested.

2.2.2 Procedure

Participants were seated in a video-controlled, electrically shielded, soundproof and air-conditioned recording room 1.2 m away from the computer screen. The visual word and form processing experiment was one of seven short experiments. The experiments were presented in pseudorandom order. Electrode positions were measured with a 3D digitizer. As compensation, each child received a small present after the study. The entire session lasted about 3.5 hours.

2.2.3 Stimuli and task

The stimuli of the word, pseudoword, symbol and picture conditions were shown in black on a white background (Fig. 1). The 72 stimuli per condition were shown in two blocks of 36 stimuli and contained 17% immediate repetitions serving as targets. The block sequence was counterbalanced (2 x 4 blocks). The participants were asked to press a mouse button with their preferred hand after an immediate stimulus repetition. The stimulus duration was 700 ms followed by a 1350 ms interstimulus interval (ISI).

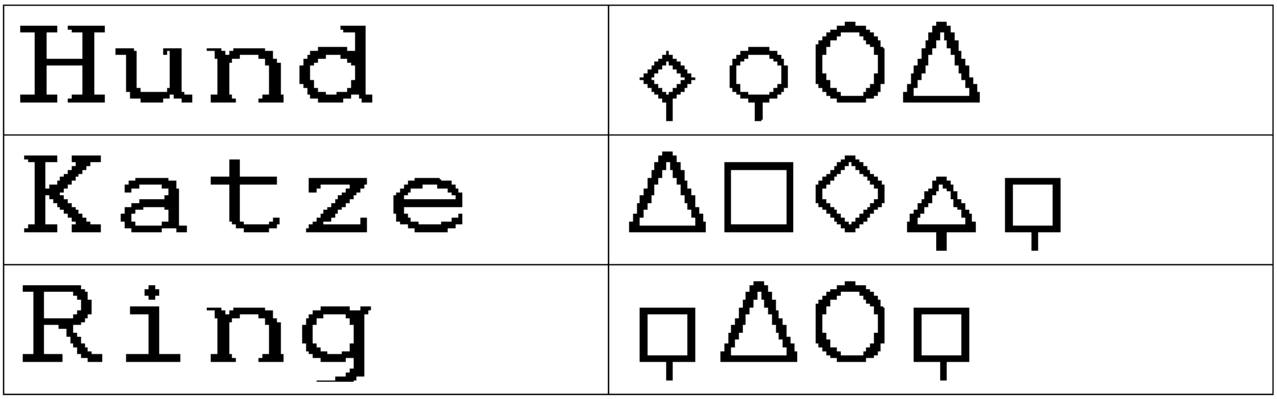

Fig. 1. Word and symbol string stimuli (examples).

Words, pseudowords and symbol strings were matched for character size (including ascenders and descenders), font size, and string length. Words and pseudowords were in lower case letters starting with an uppercase. Pictures were drawn from the Snodgrass pictures (Snodgrass and Vanderwart, 1980). Word and symbol stimuli are shown in Fig. 1. Only the results for word and symbol processing are reported in this paper.

2.2.4 ERP recording and processing

The 43 channel ERPs were recorded at 500 Hz/channel with filter settings 0.1-70 Hz and with calibrated technical zero baselines. Caps were used for the montage which included all 10-20 system electrodes plus additional electrodes: Fpz (recording reference), Oz, FT9/10, FC5/6, TP9/10, CP5/6, PO9/10, AF1/2, FC1/2, C1/2, CP1/2, PO1/2 and two EOG electrodes below the outer canthus of each eye. O1/2 and Fp1/2 were placed 2 cm more laterally for more even coverage. Impedance was kept below 20 kΩ (Ferree et al., 2001). The continuous EEG was corrected for horizontal and vertical eye movements and in some cases for slow wave artefacts. An advanced method which minimizes topographic EEG distortions was used (multiple source eye correction method; Berg and Scherg, 1994). Corrected files were digitally lowpass filtered (30 Hz, 48 dB/oct), downsampled to 256 Hz, and segmented (-125 ms prior and 1125 ms following the stimulus). Trials with artefacts exceeding ±100 μV in any

channel (1 adult ±40 μV, 2 children ±125 μV) were automatically rejected before averaging. Averaging was done separately for each condition including only non target stimuli.

ERPs were transformed to the average reference (Lehmann and Skrandies, 1980) which was used for all subsequent analyses. For each age group condition grand averages were computed. Adaptive segmentation according to GFP minima (Brandeis et al., 1994; Brandeis and Lehmann, 1998; van Leeuwen et al., 1998) was done separately for children (time range 0-1000 ms) and adults (time range 0-850 ms) because of shorter latencies in adults. The minima of the smoothed GFP (filter = 20 Hz) of the grand mean (averaged over words and symbol condition means) were used as segment borders. Additional minima in the smoothed GFP of the separate word and symbol means were also taken into account. If two minima occurred less than 50 ms apart, the more prominent one was used. The resulting segments were further analysed in each age group . For each segment, GFP and 3-dimensional (3D) location for positive and negative centroids (centre of gravity) were computed at the individual level for word and symbol conditions separately (Lehmann, 1990; Brandeis et al., 1994). GFP is a measure for the electric field strength, whereas the 3D centroids defined in Talairach coordinates (Talairach and Tournoux, 1988) represent the topography of the field.

Two overall analyses were computed for strength (GFP) and topography (3D centroids). GFP was analysed in a Multivariate Analysis of Variance (MANOVA, procedure GLM) for repeated measures with within subject factors "*segment*" (7 segments) and "*wordlike*" (words vs. symbols) and between subject factor "*agegroup*" (children vs. adults). The 3D centroids were analysed in a similar MANOVA, but with the additional factor "*polarity*" (positive vs. negative centroid). The three dimensions (x- , y- , and z-axes) were treated as multivariate dependent measures.

Post hoc analyses of differences between word and symbol maps were conducted with a topographical bootstrapping approach. Separate tests were run in each

segment, for each age group, and for both raw and amplitude-normalised maps. TANOVA (topographic analysis of variance; Strik et al., 1998; Pascual-Marqui et al., 1999) computes the exact probability of dissimilarity between two maps (Lehmann and Skrandies, 1980) using bootstrapping statistics. TANOVA on raw maps detects all systematic amplitude differences between the maps. TANOVA on normalized maps (i.e. maps scaled to unity GFP) detects only the purely topographic differences which cannot be explained by overall amplitude (GFP) differences. In addition, *t*-maps of word-symbol differences have been used for illustration. For direct comparison between age groups in specific segments, 3D centroids were analysed using a MANOVA for repeated measures as described above. For the *post hoc* MANOVAs the last four segments were averaged. For all statistic tests the significance level was set to 0.05, but trends ($p < 0.1$) of specific theoretical interest are also reported.

Source localisation with LORETA (Low Resolution Electromagnetic Tomography; Pascual-Marqui et al., 1994; Pascual-Marqui et al., 1999) was computed for each of the first 3 segments and for the averaged last 4 segments of the children's and adults' word and symbol grand mean data. LORETA computes the smoothest possible 3D distributed current source density solution, which is constrained to grey matter and which produces the measured scalp map. This distributed source solution does not need an *a-priori* number of hypothesised generators, and produces a unique but blurred solution of focal sources due to the smoothness constraint. Results are illustrated in Talairach space (Talairach and Tournoux, 1988). Less plausible LORETA solutions were recomputed within a realistic boundary element head model (CURRY-software; Fuchs et al., 2001; Fuchs et al., 2002) and compared to dipole solutions.

Behavioural data (accuracy and reaction time) were analysed computing 2 MANOVAs for repeated measures with the factors "*wordlike*" (words vs. symbols) and "*agegroup*" (children vs. adults). Accuracy values were analysed after an arc sine transformation.

2.3 Results

2.3.1 Behavior

Adults detected repetitions more accurately than children (*agegroup*, $F(1,34) = 94.66$, $p < 0.001$). This difference was larger for words than for symbols (*agegroup x wordlike*, $F(1,34) = 7.49$, $p < 0.01$). *Post hoc* tests revealed that children missed a similar percentage of word and symbol targets (words: 48.6 %, symbols: 44.8 %, $t(22) = 0.66$, p = ns), whereas adults missed far fewer words than symbols (words: 0.6 %, symbols: 9.6 %, $t(12) = -3.28$, $p < 0.01$).

Children had longer reaction times than adults (*agegroup*, $F(1,33) = 60.60$, $p < 0.001$). This difference was marginally larger for words than for symbols (*agegroup x wordlike*, $F(1,33) = 3.40$, $p < 0.1$). *Post hoc* tests revealed that children had longer reaction times for words than for symbols (words: 987 ms, symbols: 908 ms, $t(21) = 2.33$, $p < 0.05$), whereas reaction times in adults were similar for both stimulus conditions (words: 543 ms, symbols: 556 ms, $t(12) = -0.43$, p = ns).

2.3.2 ERP segmentation

To compare different stages of information processing, the ERPs were adaptively segmented. This resulted in 7 segments (s1 to s7) in both age groups, with typically longer latencies and more Global Field Power (GFP) in children than in adults (Fig. 2). While GFP essentially decreased in strength from S1 (P100) to S7 for children, the S2 (N200) and S4 (P300) to symbols showed most GFP in adults.

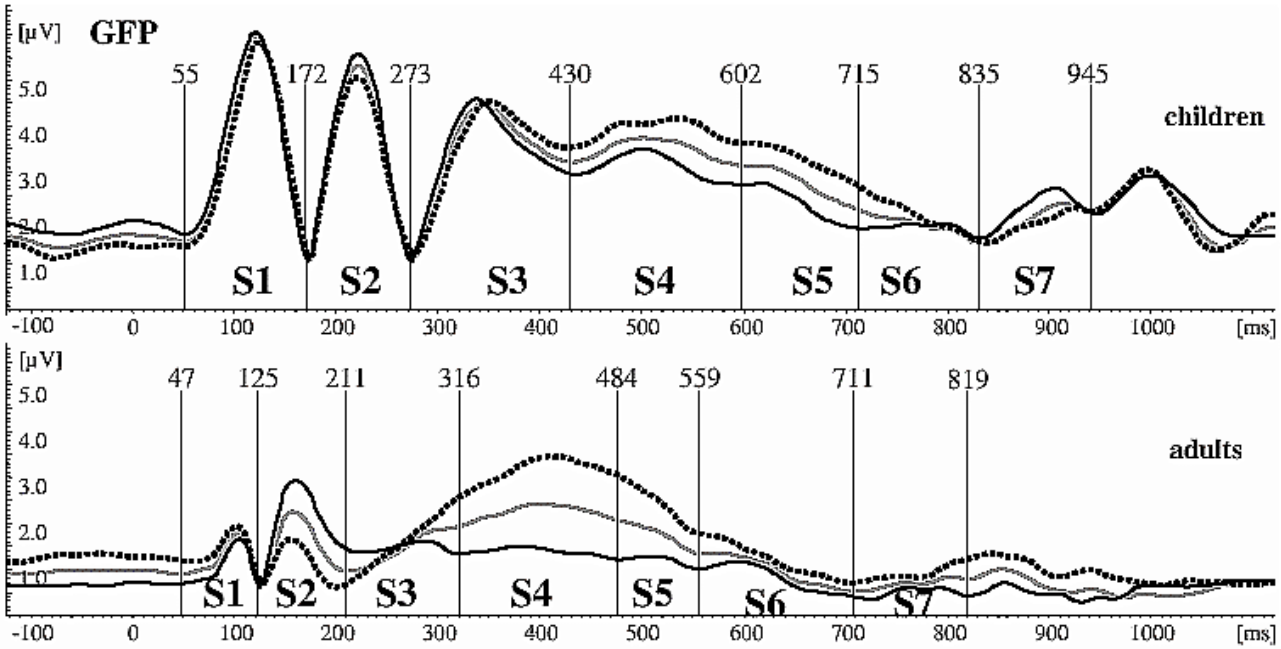

Fig. 2. Segmentation for children (top) and adults (bottom) based on GFP curves to words (black line), symbol strings (dotted line) and their average (grey line). The vertical lines between the segments (S1 to S7) depict segment borders with border latency in ms. Longer latencies and larger amplitudes are evident in children compared to adults.

2.3.3 Global ERP comparisons

GFP was used to estimate the global strength or amplitudes of the maps. To measure map topography the centers of gravity were computed for positive and negative values separately (positive and negative centroids). The term "centroid distribution" is used here, when positive and negative centroids showed a different pattern (statistical interaction with polarity), and "centroid mean location", when positive and negative centroids showed a similar pattern (no interaction with polarity).

Symbols evoked more GFP than words (*wordlike*, $F(1,34) = 13.09$, $p < 0.001$), especially in segments 4 to 6, whereas in segment 2 words had more GFP than symbols (*wordlike x segment*, $F(6,29) = 7.94$, $p < 0.001$). This pattern tended to be different between children and adults (wordlike x segment x agegroup, $F(6,26) = 2.12$, $p<0.1$), especially in segments 1, 3 and 7.

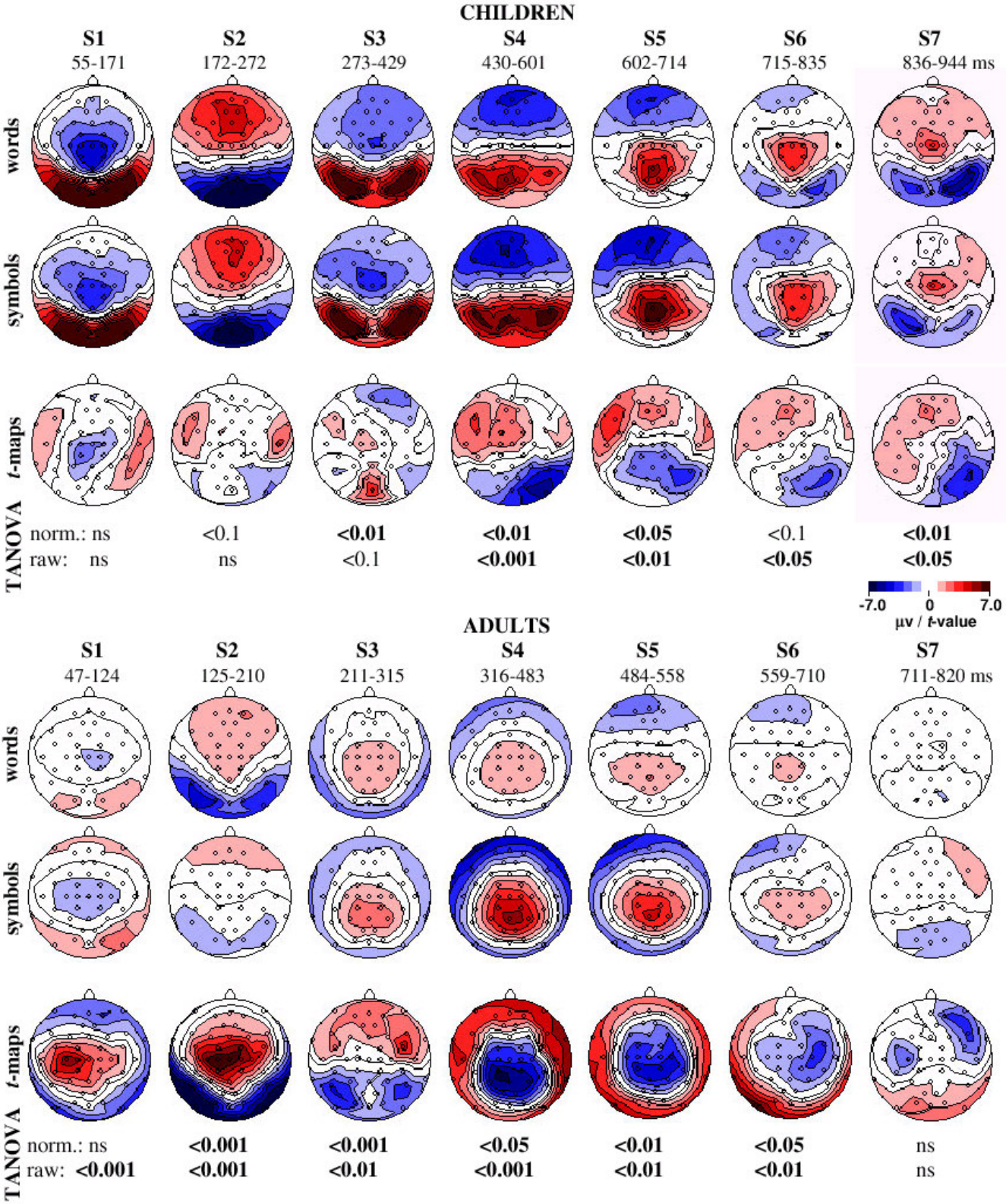

Fig. 3. ERP and *t*-maps with TANOVA significance levels. Maps seen from top, nose up. Note that adults but not children show significant word-symbol differences in the N200 segment s2. Significant word-symbol differences during the subsequent segments are present in both age groups, but with different topographies. Critical values in the *t*-maps ($p<.05$) are $t(12)=+/-2.18$ for adults and $t(22)=+/-2.074$ for children.

Children's ERP maps had more GFP than adults' (*agegroup*, $F(1,34) = 71.77$, $p < 0.001$). This difference was present in each segment, but most prominent in segment 1 and least prominent in segment 5 (*agegroup x segment*, $F(6,29) = 2.52$, $p < 0.05$).

The seven segments had different GFP, with highest values in segment 4 and lowest values in segment 7 (*segments*, $F(6,29) = 17.96$, $p < 0.001$). As already described the GFP values in the 7 segments were affected by stimulus condition and age group.

Centroid distribution differed between the word and symbol conditions (*wordlike x polarity*, $F(3,32) = 3.09$, $p < 0.05$). Centroid mean locations of words and symbols changed differently across the 7 segments (*wordlike x segment*, $F(18,17) = 3.79$, $p < 0.01$). Most importantly, the distinct centroid trajectories after word and symbol presentation, which were polarity dependent, were not the same for children and adults (*wordlike x segment x agegroup x polarity*, $F(18,17) = 3.21$, $p < 0.05$).

Centroid mean location and distribution differed between children and adults (*location: agegroup*, $F(3,32) = 7.14$, $p < 0.001$; *distribution*: *agegroup x polarity*, $F(3,32) = 7.90$, $p < 0.001$). These age group differences varied across the 7 segments (*agegroup x segment*, $F(18,17) = 4.13$, $p < 0.01$; *agegroup x segment x polarity*, $F(18,17) = 9.33$, $p < 0.001$).

Centroids were different between the 7 segments (*segment*, $F(18,17) = 10.65$, $p < 0.001$; *segment x polarity*, $F(18,17) = 227.29$, $p < 0.001$). There was also a time invariant difference between positive and negative centroid locations (*polarity*, $F(3,32) = 12.69$, $p < 0.001$).

2.3.4 Post hoc ERP comparisons

The *wordlike x segment x agegroup x polarity* interaction was followed by comparisons within individual segments. Topographic Analyses of Variance (TANOVA) were used for within group comparison and centroid statistics for between group comparison.

In segment 1 (P100 component), word and symbol maps were not significantly different in children (TANOVA on both normalised and raw maps, Fig. 3). Furthermore, normalised word and symbol P100 maps did not differ in adults (Fig. 3). However, adults' raw maps differed at the $p < 0.001$ level (Fig. 3). This can also be seen in the *t*-maps. Adults showed a central left lateralised positive difference between words and symbols due to more negative values over central sites in the symbol condition (Fig. 3).

Table 1. Post hoc segmentwise GFP and topography comparisons between word and symbol stimuli, children and adults (significant effects).

Segment	GFP	Topography			
		Centroid mean location		Centroid distribution	
		Multivariate	Axis	Multivariate	Axis
s1	**G**, *F(1,34) = 94.70* ***	**G**	Y	**G x P**, *F(3,32) = 3.48* *	Y
	W x G, *F(1,34) = 7.88* **	F(3,32) = 7.11 ***			
s2	**G**, *F(1,34) = 41.55* ***	**W**, *F(3,32) = 5.14* **	Y	**W x P**, *F(3,32) = 4.11* *	Z
		G, *F(3,32) = 3.28* *	all ns	**W x G x P**, *F(3,32) = 6.71* **	Z
		W x G, *F(3,32) = 3.31* *	Y		
s3	**G**, *F(1,34) = 20.93* ***			**G x P**, *F(3,32) = 45.52* ***	Y, Z
				W x G x P, *F(3,32) = 4.94* **	X, Y
s4-7	**G**, *F(1,34) = 35.89* ***	**G**, *F(3,32) = 6.80* **	Y, Z	**W x P**, *F(3,32) = 5.02* **	X, Z
(averaged)	**W**, *F(1,34) = 27.47* ***			**W x G x P**, *F(3,32) = 7.06* ***	Y, Z

W = *wordlike*; G = *agegroup*; P = *polarity*; x = interaction; X, Y, Z = univariate significant axis (X = left-right, Y = anterior-posterior, Z = superior-inferior); * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$; *polarity* main effects have not been included in this table, since they had different centroid distribution in each segment (all $p < 0.01$).

Children's raw maps to words and symbols in segment 2 (N200 component) were not different (TANOVA on raw maps, p = ns, Fig. 3). However, their normalised word and symbol maps were marginally different (TANOVA on normalised maps, p

< 0.1, Fig. 3). In contrast, adults' word and symbol maps differed at a high significance level (TANOVA on both normalised and raw maps, $p < 0.001$, Fig. 3). As the *t*-maps illustrate, word-symbol differences in adults were due to increased occipitotemporal negativities and a central positivity to words (Fig. 3).

The centroid mean location was more anterior for symbols than for words (table 1: segment 2, *W, y-axis*). This was more pronounced for adults than for children (table 1: segment 2, *W x G, y-axis*). The centroid distribution was different between words and symbols with the positive word centroids located higher and the negative word centroids located lower than the corresponding symbol centroids (table 1: segment 2, *W x P, z-axis*). This difference between positive and negative word centroids was larger in adults than in children. In contrast in the symbol condition, positive centroids were located higher than negative centroids only in children and not in adults (table 1: segment 2, *W x G x P, z-axis*).

Segment 3 was the first segment in which children's normalised word and symbol maps were significantly different (TANOVA on normalised maps, $p < 0.01$, Fig. 3). However, their raw maps were only marginally different (TANOVA on raw maps, $p < 0.1$, Fig. 3). As illustrated by the *t*-maps (Fig. 3), the word-symbol difference consisted mainly of a focussed posterior positivity at electrode Oz and of a right anterior negativity. In adults, word and symbol maps were also different (TANOVA on normalised maps, $p < 0.001$, and on raw maps, $p < 0.01$, Fig. 3).

A direct comparison between children and adults revealed that in children the positive centroids were located more posterior and lower than in adults, whereas the negative centroids were more anterior and higher (table 1: segment 3, *G x P, y- and z-axes*). Positive word centroids were located further to the right in adults than in children, whereas the positive symbol centroids were located at similar positions on the right side in both age groups. Accordingly, negative word centroids were located on the left in adults and on the right in children, whereas for negative symbol centroids the opposite pattern was true (table 1: segment 3, *G x W x P, x-axis*). In adults, the positive word centroid was more anterior than the negative word centroid, whereas for the symbol centroids the opposite was true. In contrast, children's

positive centroids were more posterior than negative centroids for both stimulus conditions (table 1: segment 3, *G x W x P, y-axis*).

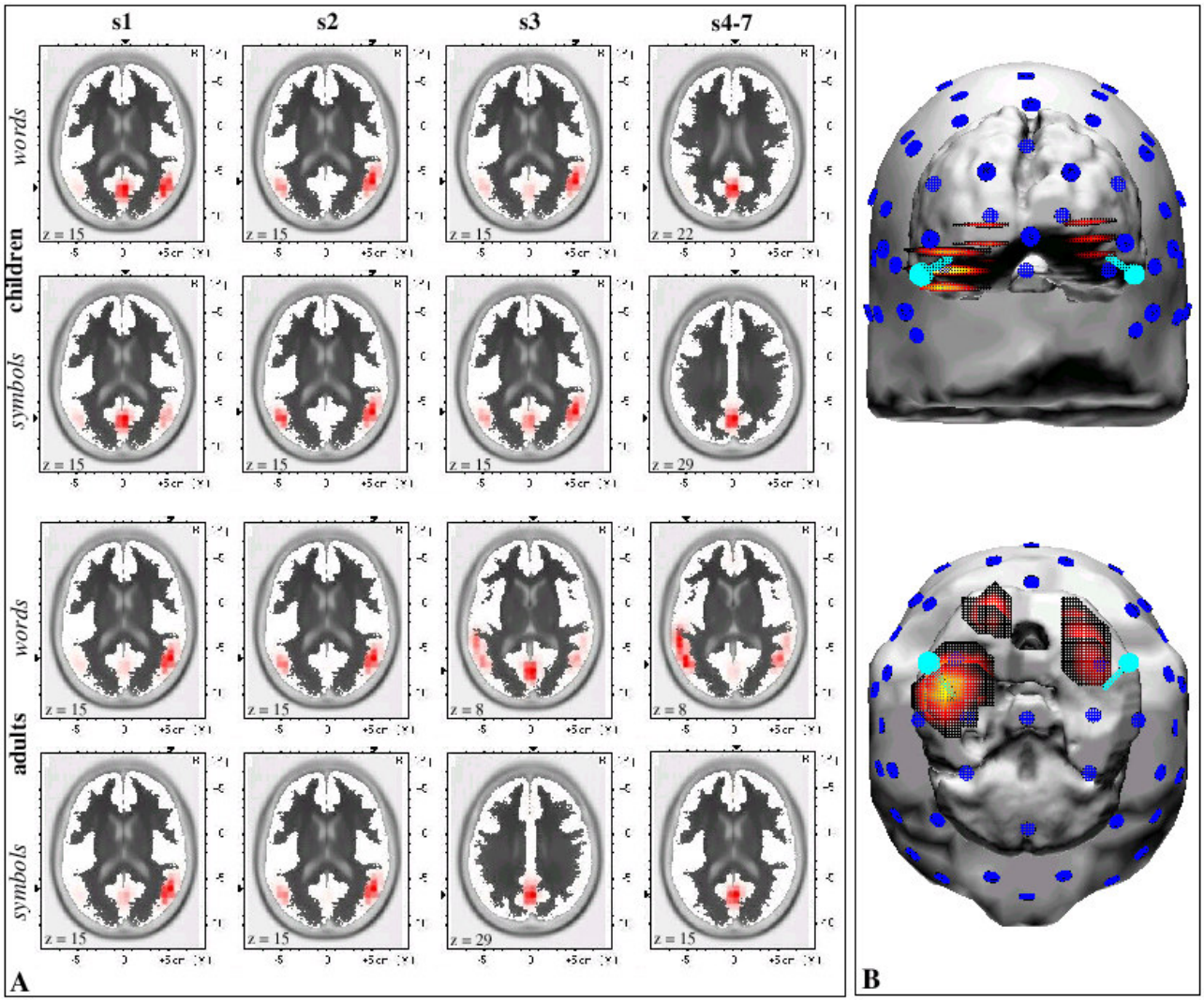

Fig. 4A. Local maxima of LORETA sources (spherical head model, filtered 1.5-30, regularisation factor 0.001). Differences between children and adults activation patterns are prominent in the later segments, particularly for words (s3 and s 4-7) but also for symbols (s3). Z-coordinates (in Talairach coordinates) are printed within each slice.
Fig. 4B. LORETA sources (on slices) and mirror-symmetric dipoles (cyan colour) using a realistic head model for the word-N200 in adults; warped brain with skin and electrodes (dark blue) from the back (top) and from below (bottom, nose downwards). In addition to 2 bilateral occipital LORETA sources, a deeper and left lateralised third source cluster was found near the VWF area in the left fusiform gyrus. The dipole in the left hemisphere is located nearby.

In the last four segments children's word and symbol maps were significantly different (TANOVA on both normalised and raw maps, except for a trend in segment 6 (Fig. 3). Similarly, word-symbol differences occurred in adults in the remaining segments (TANOVA on both normalised and raw maps, $p < 0.05/0.01/0.001$, Fig. 3),

except for the last segment. Word-symbol differences in children were most prominent at right occipitotemporal electrodes, where the word condition elicited less positive or more negative values (see *t*-maps, Fig. 3). In contrast word-symbol differences in adults were most prominent as a central negativity reflecting the smaller P300 for words than for symbols.

For direct comparison of word-symbol differences between children and adults the last four segments (s4-s7) were averaged. For symbols the positive centroid was left-lateralized and the negative centroid right lateralized, while words showed a reversed, less pronounced asymmetry (table 1: averaged segments 4-7, *W x P, x-axis)*. The positive symbol centroid was located higher, and the negative symbol centroid lower than the corresponding word centroids (table 1: averaged segments 4-7, *W x P, z-axis).* Positive centroids were always located posterior to the negative centroids. This centroid distance was larger for words than for symbols in adults, whereas in children it was larger for symbols than for words (table 1: averaged segments 4-7, *G x W x P, y-axis)*. Positive centroids were also always located higher than negative centroids. This was more pronounced for symbols than for words in adults, but not in children (table 1: averaged segments 4-7, *G x W x P, z-axis;* reflecting the prominent symbol-P300 in adults but not in children).

An additional analysis was conducted to investigate the time course of N200 lateralisation effects in adults. Hence, segment 2 was divided into thirds and tested for hemispheric asymmetries at occipitotemporal sites (O1/2, PO9/10, T5/6, similar to Bentin et al., 1999) using a MANOVA for repeated measures with factors "*third*", "*wordlike*", and "*hemisphere*" treating electrode site as independent measures. Results revealed a significant "*third x wordlike x hemisphere*" interaction ($F(6,7) = 4.22$, $p < 0.05$) beside the expected "*wordlike*" effect ($F(3,10) = 29.49$, $p < 0.001$). Testing each third separately revealed that negativity was more left lateralised in words than symbols in the 2 last thirds of the N200 segment (2nd third: *wordlike x hemisphere,* $F(3,10) = 4.23$, $p < 0.05$; 3rd third: *wordlike x hemisphere,* $F(3,10) = 4.01$, $p < 0.05$). In contrast this interaction was not significant in the 1st third of segment 2 (*wordlike x hemisphere,* $F(3,10) = 0.89$, $p =$ ns).

An additional analysis was conducted to estimate the influence of children's letter knowledge. We divided the children into two letter knowledge groups (n = 12, 0-11 letters named; n = 11, 12 or more letters named). The analyses focused on group differences at those electrodes yielding the most significant word-symbol difference during the N200 and subsequent microstates (right posterior-temporal electrode T6 in segment 2 and averaged segments 4-7, midoccipital electrode Oz in segment 3). In segment 2 the amplitude at T6 tended to be more negative in the word than in the symbol condition (*wordlike*, $F(1,21) = 4.18$, $p < 0.1$). This was more pronounced in the high letter knowledge group, whereas the low letter knowledge group showed equal amplitudes for word and symbol conditions (*wordlike x letter knowledge group*, $F(1,21) = 4.50$, $p < 0.05$). In segment 3 and the averaged segments 4-7 word-symbol differences were significant (*wordlike*, $F(1,21) = 16.81$, $p < 0.001$; $F(1,21) = 26.26$, $p < 0.001$, respectively) but not influenced by letter knowledge (*wordlike x letter knowledge group*, $F(1,21) = 1.28$, p = ns; $F(1,21) = 0.10$, p = ns, respectively).

Table 2. Talairach coordinates of maximal LORETA source in the segments.

Segment	Children		Adults	
	words (x, y, z, strength)	symbols (x, y, z, strength)	words (x, y, z, strength)	symbols (x, y, z, strength)
s1	4, -67, 15; 0.00589	4, -67, 15; 0.00564	53, -60, 15; 0.00260	53, -60, 15; 0.00238
s2	53, -60, 15; 0.01038	53, -60, 15; 0.00924	53, -60, 15; 0.00448	53, -60, 15; 0.00316
s3	53, -60, 15; 0.00484	53, -60, 15; 0.00478	4, -74, 8; 0.00152	4, -67, 29; 0.00137
s4-7 (averaged)	4, -67, 22; 0.00234	4, -67, 29; 0.00236	-52, -67, 8; 0.00077	4, -67, 15; 0.00129

Segments 4 to 7 were averaged before computation.

LORETA solutions computed in a spherical head model are illustrated in Fig. 4A for the first 3 segments and the averaged segments 4 to 7. Source solutions for children's word and symbol maps were quite similar. In adults the sources for the

P100 and N200 look also quite similar. However, in segment 3 and averaged segments 4-7 their word maps showed (among other sources) left anterior superior temporal sources (including Brodmann Area 22), which were neither detected for symbol maps in adults, nor for either word or symbol maps in children (Fig. 4A, table 2). Adult's N200 sources were located in posterior bilateral middle/superior temporal cortex. A localization within one cm of the VWF area, and a prominent left lateralisation was found only with a realistic head model (Fig. 4B). Children's word map sources in the last 4 segments were located in posterior areas (near the visual cortex). The LORETA and dipole solutions of the adults' N200 computed with a realistic head model are illustrated in Fig. 4B. These more realistic N200 sources were also in bilateral posterior temporal cortex, but now located lower and closer to the fusiform gyrus, and also characterised by a prominent left lateralization.

2.4 Discussion

In this ERP mapping study, we investigated visual word processing of kindergarten children who could not yet read words, using a word and symbol string repetition detection task. We compared performance and 7 ERP segments of children with those of skilled adult readers using ERP measures for strength (GFP) and topography (3D centroids). Adults proved more accurate than children, but missed more symbol targets than word targets. They probably coded the words more efficiently at higher (lexical or semantic) level. In contrast, the children missed word and symbol targets equally often indicating that a more efficient strategy to process words (reading) is not yet available. The electrophysiological data revealed that children had longer latencies as reflected in the different segment borders, and more GFP plus differerent topographies than adults across both conditions. This is in agreement with other developmental studies reporting larger amplitudes and longer latencies for children than for adults along with different topographies (Kok and Rooijakkers, 1985; Taylor and Smith, 1995; Taylor and Keenan, 1999). While GFP did not reflect word-symbol

processing differences between the two age groups, topographic ERP measures detected such differences, both in the overall analysis and at the individual segment level.

Word and symbol maps of adult readers were clearly different for the N200 component (125-210 ms, segment 2). Words showed a distinct topography with increased GFP. This early word or letter specific activation is in agreement with other neurophysiological studies relating the N200 component to specialised early visual word processing in explicit (Allison et al., 1994; Tarkiainen et al., 1999) and implicit reading (Bentin et al., 1999).

In contrast the kindergarten children's N200 word and symbol maps were not different in their absolute topography and were only marginally different in their relative topography. Accordingly, the children may not yet have developed specialised areas for early visual word processing. However, the marginal negative differences found at occipitotemporal electrodes were similar to the adults' differences, although predominantly at the right hemisphere sites. This may indicate that automatisation was already beginning to develop in these children. Interestingly this marginally significant difference at the childrens' right occipitotemporal electrode T6 was influenced by letter knowledge. Children with low letter knowledge had similar amplitudes for words and symbols, whereas children with high letter knowledge had significantly more negative values for words than for symbols. This result may be related to a right hemispheric involvement in learning to read, as suggested by Licht et al. (1986) who had used a word naming and picture recognition task. They reported that children with a higher reading acquisition score (they learned the 4 tested words faster) had at the right hemisphere sites smaller N380 and larger slow wave (SW) components. Both these components were later than the N200 segment, which was not investigated. In contrast, in our data letter knowledge had no influence on word-symbol differences in the segments occurring after the N200.

The adults' N200 in this study was more left lateralised for words than for symbols consistent with Bentin et al. (1999). The lack of such asymmetry in the children's N200 strongly suggests that it results from late plasticity due to reading acquisition.

The absence of such lateralisation in adults during the initial part of the N200 segment is in agreement with Cohen et al. (2000) who demonstrated that a left lateralisation occurred only during the latter part of the N200. When using a realistic head model, LORETA and dipoles located N200 activation for word processing in inferior posterior temporal cortex near fusiform gyrus. LORETA also indicated a strong left lateralisation. This solution is in good agreement with Tarkiainen et al. (1999) who located their MEG sources for the equivalent time segment in the inferior occipitotemporal cortex, predominantly in the left hemisphere. Similarly, fMRI studies located word related activity in the left fusiform gyrus (Cohen et al., 2000; Cohen et al., 2002). Using LORETA with a spherical head model resulted also in posterior temporal solutions, but more bilaterally and in more superior temporal regions (see also Michel et al., 2001). This discrepancy would be consistent with the results from a simulation study where both the localizations errors of a spherical model, and the improvement with a realistic head model were most prominent for inferior temporal sources (Fuchs et al., 2002). However, as left VWF area activation has not been observed in all visual language tests and may be less robust in event-related designs (Cohen et al., 2002), further work with more accurate source modelling based on individual MRI, and possibly with simultaneous fMRI should clarify this issue.

Children's word and symbol maps became clearly different in the subsequent segment 3 (273-429 ms), showing a focused positive mid-occipital difference. These robust differences were independent of letter knowledge. Furthermore, the 2 maps remained different for the next 4 segments with a prominent right occipitotemporal negative word-symbol difference. The adults' maps also differentiated words and symbols in the remaining segments except the last one. However, the topographies of the late difference maps in children and adults showed little resemblance, indicating that children differentiated words from symbols in another way than adults did.

Kok & Rooijakkers (1985) had found differences between word naming and picture recognition only in a late slow wave component (SW) for both kindergarten children and adults, but not in earlier components (P280 and N500 in children, P340

in adults). To understand this apparent discrepancy, we visually compared their four channel wavewhapes to the corresponding waveshapes in our data (parietal P3/4 and temporal T3/4 electrodes, after identical signal pre-processing). Our wave forms for word and picture conditions (not reported here) were quite similar to theirs up to about 400 ms. However, in contrast to Kok & Rooijakkers (1985), word-picture amplitude differences for the children's P280 and adults' P340 were evident in our data. This may indicate that our more difficult test (repetition detection vs. naming; 60 vs only 4 words, and shorter ISI) was more likely to bring out early processing differences. Furthermore, the earliest component visible with this montage in children was the P280 which occurrs distinctly after the N200. Clearly, an extended montage with posterior temporal electrodes is essential to measure the N200 which is important in early visual word processing.

Interestingly, children's prominent right occipitotemporal negative word-symbol difference during the last 4 segments remained stable despite the changing word and symbol maps in these segments. In the segments 4 and 5 the negative difference was due to less positive right occipitotemporal values for words, whereas in the last two segments word maps showed more negative values at these sites.

In segment 3 and averaged segments 4 to 7 LORETA consistently located adults' word map sources in the left superior temporal lobe, which is commonly known to be involved in higher language processing. These activations were absent in LORETA source solutions for adults' symbol maps or children's word and symbol maps. The children's sources for words in the last 4 segments were located in medial occipital regions, indicating continued visual rather than higher language processing.

In our data, adults' word and symbol maps were already different at the level of the P100 component (segment 1) in their raw maps, but not in their normalised topography. P100 is commonly known to be sensitive for basic visual stimulus properties as word or character size or string length. Since word and symbol string stimuli were matched for these features in our experiment, we do not believe that differences in basic stimulus properties are responsible for this early word-symbol difference. Instead, this difference might reflect a very early stage of specialised

orthographic processing. Alternatively, the blockwise presentation with fixed intervals could have led to increased preparation, reflected by larger GFP to symbols than to words. This would be consistent with the increased error rate for symbols compared to words in adults, reflecting a more difficult task, and a larger P300 component (associated with more perceptual resource allocation; Isreal et al., 1980) for symbols than for words. In contrast, the children did not show a difference between word and symbol processing in the P100 component and missed word and symbol targets equally often.

In conclusion kindergarten children's N200 component did not yet reliably distinguish words from symbols in contrast to adults. Thus, kindergarten children may not yet have specialised visual areas for automatised word or letter processing before they learn to read words, despite their limited letter knowledge. This clearly demonstrates the plasticity of the N200 difference between words and symbol strings. However, their ERP segments following the N200 indicate that they already differentiated words from symbols. LORETA localised word sources for adults' late segments in left superior temporal cortex, but in visual cortex for children's segments. Thus, these differences may reflect a distinct visual precursor stage of word reading, and may indicate that implicit learning to read starts well before actual training.

3. Development of the automatic mismatch response: from frontal positivity in kindergarten children to the mismatch negativity [2]

3.1 Introduction

Unattended but perceptible auditory change elicits an automatic mismatch response in the event related potential (ERP). In adults, this automatic mismatch response usually consists of a frontocentral negative / mastoid positive "mismatch negativity" (MMN) to auditory deviance at a latency of 100 - 250 ms (Näätänen et al., 1978). It is often measured as the difference ERP between rare deviants and the embedding trains of frequent standards. Sources of the MMN have been located mainly in the bilateral auditory cortex, with some evidence for additional frontal sources (Alho, 1995). The MMN gets smaller or even disappears as the degree of deviance is reduced (Näätänen et al., 2001b). Particularly in children, this early MMN, can be followed by a late MMN peaking between 400 and 500 ms (Korpilahti et al., 1995; Korpilahti et al., 2001). In addition, irrelevant or ignored deviants or "novels" elicit a frontocentrally positive deviant-standard difference called P3a between 200 and 350 ms in adults (Squires et al., 1975) and children (Gumenyuk et al., 2001). MMN is attenuated in a wide range of disorders (e.g.: schizophrenia: Javitt et al., 2000; dyslexia: Baldeweg et al., 1999; ADHD: Rothenberger et al., 2000). An attenuated MMN to phonemes in dyslexic children has been reported also for the late MMN (Schulte-Körne et al., 1998). Since MMN tests automatic auditory processing it can be employed even with subjects who have difficulties following experimental instructions, such as young children. Since the MMN is only a small ERP component, large numbers of stimuli have to be presented resulting in long experimental sessions. One way to reduce the

[2] *Maurer et al. (2003). Clinical Neurophysiology, 11, 808-817.*

duration of the MMN recordings is to use short stimulus onset asynchronies (SOA; onset to onset interval). Additionally, small deviances might be better suited than large deviances to detect subtle auditory processing deficits.

MMN has been reported to be quite stable during development. Studies investigating school children reported MMN responses similar to adults with slightly longer latencies (Gomes et al., 1999; Gomes et al., 2000; Gomot et al., 2000; Shafer et al., 2000). Furthermore, younger children had longer latencies than older children (Gomes et al., 1999; Gomot et al., 2000; Shafer et al., 2000). Studies investigating 5-8 year olds reported MMN peak latencies between 190 and 270 ms for frequency deviance (Cheour et al., 1997; Holopainen et al., 1997; Gomes et al., 1999; Gomot et al., 2000; Shafer et al., 2000) and between 180 and 350 ms using phoneme or word deviance (Kraus et al., 1999; Korpilahti et al., 2001; Cheour et al., 2002). Using hard, medium and easy deviants (1050, 1200, 1500 Hz vs. 1000 Hz standard) in 8-12 year olds, Gomes et al. (2000) reported an MMN only for medium and easy deviants, but not for hard deviants, when the children were ignoring the stimuli. A significant MMN for hard deviants was only elicited when they actively attended to the stimuli. Adults showed an MMN for all 3 deviants under the ignore condition, but the MMN amplitudes were smaller with smaller deviance and were not influenced by attention (Gomes et al., 2000). Investigating 7-9 year olds using 3 different SOAs (450, 800, 1500 ms) in a frequency MMN paradigm, Ceponiené et al. (1998) reported no significant differences in MMN amplitude or latency between the three SOA conditions. In contrast to the MMN (an ERP difference), the components of the ERP to standards was affected by the different SOAs in the same study. With short SOA children showed a P100-N200 sequence, which is typically observed in children (Sharma et al., 1997; Albrecht et al., 2000; Pang and Taylor, 2000; Ponton et al., 2000). However, with the longer SOAs additional components emerged, which made the children's ERP component sequence more similar to the P1-N1-P2-N2 sequence which is typically observed in adults. Similarly in adults, short SOA (400 ms) enhanced P1 and reduced N1 compared to long SOA (1000 ms), whereas frequency MMN was not affected by SOA manipulation (Schröger, 1996).

The MMN can be elicited even in newborns and infants (e.g. Cheour-Luhtanen et al., 1995). However, some infant studies reported a positive deflection instead of a negative one using frequency (Morr et al., 2002) or phoneme deviants (Dehaene-Lambertz, 2000). Morr et al. (2002) reported a positivity for infants up to 12 months using a medium deviance (deviant: 1200 Hz, standard: 1000 Hz), whereas in children up to 4 years, no deviant-standard difference, and thus also no MMN, was present. However, using a very large deviance (deviant: 2000 Hz, standard: 1000 Hz) the authors reported an MMN in nearly all of the children, while in infants up to 12 months the MMN was followed by a large frontal positivity. The authors suggested that the MMN had been masked by this positivity to a different extent according to age and deviant size (Morr et al., 2002). In contrast to these infant studies, such positive deflections replacing an MMN have not been reported in studies with older children.

The aim of the present study was to apply an MMN-paradigm with time-saving short SOA and small deviance in kindergarten children and to compare their automatic mismatch response with adults' mismatch response.

3.2 Methods

3.2.1 Subjects

Kindergarten children without familial risk for dyslexia (n = 29, mean ±SD years = 6.5 ±0.38, 15 males and 14 females, 4 left handed) and healthy adults (n = 24, mean ±SD years = 26.6 years ±3.15, 11 males and 13 females, 5 left handed) participated in this study. Children and their families were contacted in their kindergarten. All parents signed an information and consent form explaining the study and stating that the child is free to leave the study at any time and for any reasons. All kindergarten children were tested for intelligence (CFT-1; Weiss and Osterland, 1997), phonological abilities (BISC; Jansen et al., 1999), letter and word reading abilities,

and visual and auditory acuity. Parents also filled out the Child Behavior Checklist (CBCL; Achenbach and Edelbrock, 1983). About one and a half week (mean = 11.4, range = 4 to 55 days) later, the ERP measurement was acquired at the Brainmapping Laboratory. Two children with a phonological risk for dyslexia (BISC risk points > 3) were excluded from the entire analysis. One adult man had a tinnitus. It will be reported in the results if an exclusion of this subject would have altered the results. All children had an IQ above 85 points (mean ±SD= 107.7 ±13.7). All remaining participants had normal visual and auditory acuity.

3.2.2 Procedure

Participants were seated in a video-controlled, electrically shielded, soundproof and air-conditioned recording room 1.2 m away from the computer screen. The frequency and phoneme MMN-paradigms were 2 of 7 experiments. The order of the 2 MMN experiments was counterbalanced, all 7 experiments were presented in pseudorandom order. Electrode positions were measured with a 3D digitizer. As compensation, each child received a small present after the study. The entire session lasted about 3.5 hours including a warming-up phase to get the child acquainted with the two experimenters at the beginning, electrode cap attachment while the child watched a video, and breaks according to the individuals need with conversation, eating and drinking.

3.2.3 Stimuli

Frequency and phoneme stimuli were presented in separate experiments. The auditory frequency stimuli consisted of one standard (1000 Hz) and two deviant tones (larger deviant: 1060 Hz, smaller deviant: 1030 Hz). The phoneme stimuli were also one standard (‘ba’) and two deviants (larger deviant: ‘ta’, smaller deviant: ‘da’) naturally spoken by the same female voice (professional speaker) and matched for

duration and peak amplitude. The stimuli were 100 ms in duration (including 5 ms rise and fall) and were presented binaurally by speakers at 78dB placed on the ground 2.30 m in front of the subject. Stimuli were presented with a 383-ms stimulus onset asynchrony (SOA). Stimulus order was pseudorandomized with not less than two standards between two deviants. The percentage of the deviants was 16.66 % equally distributed for the two deviants (1500 standards, 150 larger deviants, 150 smaller deviants per experiment). Participants sat quietly and ignored the stimuli. Children watched videos or played Gameboy, all adults played Gameboy. All games or videos were either silent or set to a low sound level.

3.2.4 Discrimination task

The same stimuli were grouped into trains (trials) for the behavioral discrimination performed by all children and by 20 adults. 80 stimulus trains, each consisting of 6 stimuli, were presented. All stimuli within a train were standards except the 4^{th} stimulus which could be a standard (50%) or one of the two deviants (25% each). The subjects were not informed about the deviant position within a train in order to keep the test as similar as possible to the MMN part. The within-train SOA was the same as for the EEG experiment. Two trains were separated by 800 ms (ISI) taking account for reaction time. The subjects had to press a mouse button, whenever they perceived a deviant stimulus. A visual feedback (blue print = correct, red print = incorrect) was given for each response. Separate discrimination tasks were run for tones and phonemes. Children were tested about one and a half weeks before the EEG recording, adults were tested in a separate session some weeks after the EEG recording or at the beginning or at the end of the EEG recording.

3.2.5 ERP recording and data analysis

The 43 channel ERPs were recorded at 500 Hz/channel with filter settings 0.1-70 Hz and with calibrated technical zero baselines, but without further prestimulus baseline adjustment to avoid distorting map and source topographies (Lehmann and Skrandies, 1984). Caps (Easy Cap, FMS, Munich) were used for the montage which included all 10-20 system electrodes plus additional electrodes: Fpz (recording reference), Oz, FT9/10, FC5/6, TP9/10, CP5/6, PO9/10, AF1/2, FC1/2, C1/2, CP1/2, PO1/2 and two EOG electrodes below the outer canthus of each eye. O1/2 and Fp1/2 were placed 2 cm more laterally for more even coverage. Impedance was kept below 20 kΩ (Ferree et al., 2001). The continuous EEG was corrected for horizontal and vertical eye movements and in some cases for slow wave artefacts. An advanced method which minimizes topographic EEG distortions was used (multiple source eye correction method msec; Berg and Scherg, 1994). Corrected files were digitally lowpass filtered (30 Hz, 48 dB/oct), downsampled to 256 Hz, and segmented (-125 ms prior and 1000 ms following the stimulus). Trials with artefacts exceeding ±100 μV in any channel were automatically rejected before averaging. Averaging was done separately for standard and two deviants of each stimulus type.

The ERPs were transformed to the average reference (Lehmann and Skrandies, 1980) which was used for all subsequent analyses. Individual differences between the two deviants and the standard (mismatch responses), and grand averages for standard, deviants and differences were computed.

To assess the mismatch response, standard and deviant ERP maps were first compared with a topographical bootstrapping approach (4 comparisons at each time point in each age group). TANOVA (topographic analysis of variance; Strik et al., 1998; Pascual-Marqui et al., 1999) computes the exact probability of dissimilarity between two maps (Lehmann and Skrandies, 1980) using bootstrapping statistics. TANOVA on raw maps detects all systematic amplitude differences between the maps. For direct comparison of the mismatch response between adults and children we selected the longest period which was centred between 150 and 300 ms for

children and between 100 and 250 ms for adults (to accommodate the longer latencies of children), and which exhibited a continuous and consistent mismatch response. This latter criterion required significant successive deviant-standard map differences in all four running TANOVA comparisons. All subsequent analyses were performed on the mismatch response reflected by difference maps (deviant-standard). After averaging the mismatch response over these periods, Global Field Power (GFP) and 3D centroids (centre of gravity for positive and negative map regions) were computed at the individual level for each deviance and stimulus type separately (Lehmann, 1990; Brandeis et al., 1994). GFP is a measure for the electric field strength, whereas the 3D centroids represent the topography of the field. The 3D centroid locations were defined in Talairach coordinates (Talairach and Tournoux, 1988).

GFP and location of the 3D centroids were analysed in two separate overall Multivariate Analyses of Variance (MANOVA, procedure GLM) for repeated measures with within subject factors "*stimulus type*" (tones vs. phonemes), "*deviance*" (larger vs. smaller) and "polarity" (centroids only, positive vs. negative centroid) and between subject factor "*age group*" (children vs. adults). The 3 location dimensions (x-, y-, and z-axis) were treated as multivariate dependent measures. For all statistical tests the significance level was set to 0.05. Trends ($p < 0.1$) of specific theoretical interest are also reported.

Source localisation with LORETA (Low Resolution Electromagnetic Tomography; Pascual-Marqui et al., 1994; Pascual-Marqui et al., 1999) was computed for the difference ERP grandmeans for each age group and stimulus type separately. Difference ERP grandmeans of the 2 deviants were averaged. LORETA computes the smoothest possible 3D distributed current source density solution, which is constrained to grey matter and which produces the measured scalp map. Furthermore, LORETA does not need an *a-priori* number of hypothesised generators, but produces a blurred solution of focal sources due to the smoothness constraint. Results are illustrated in Talairach space (Talairach and Tournoux, 1988).

Accuracy results from the behavioral discrimination task were transformed into *d'* sensitivity measures and analysed in a MANOVA for repeated measures with within

subject factors "*stimulus type*" (tones vs. phonemes) and "*deviance*" (larger vs. smaller) and between subject factor "*age group*" (children vs. adults).

3.3 Results

3.3.1 Behavioral discrimination

Children were less accurate (*d'* = 2.65) than adults (*d'* = 4.34) at discriminating deviants from standards (*age group*, $F(1,45) = 123.56$, $p < 0.001$), particularly for tones (*age group x stimulus type*, $F(1,45) = 16.40$, $p < 0.001$). Phonemes were better discriminated than frequencies (*stimulus type*, $F(1,45) = 15.92$, $p < 0.001$). However post hoc analysis revealed a significant difference between frequency and phoneme discrimination only in children (frequency-*d'* = 2.03, phoneme-*d'* = 3.27, *stimulus type*, $F(1,26) = 23.53$, $p < 0.001$), but not in adults (frequency-*d'* = 4.34, phoneme-*d'* = 4.33; *stimulus type*, $F(1,19) = 0.01$, p = ns). Furthermore, larger deviance was more accurately discriminated than smaller deviance (*deviance*, $F(1,45) = 14.55$, $p < 0.001$).

3.3.2 Mismatch response

The period during which standard and deviant ERP maps for all 4 conditions (2 stimulus types, 2 deviants each) differed in children was between 179 and 207 ms (Fig. 5). The corresponding period in adults was between 129 and 199 ms (Fig. 5). These periods were used for direct comparison between children and adults in the overall analyses.

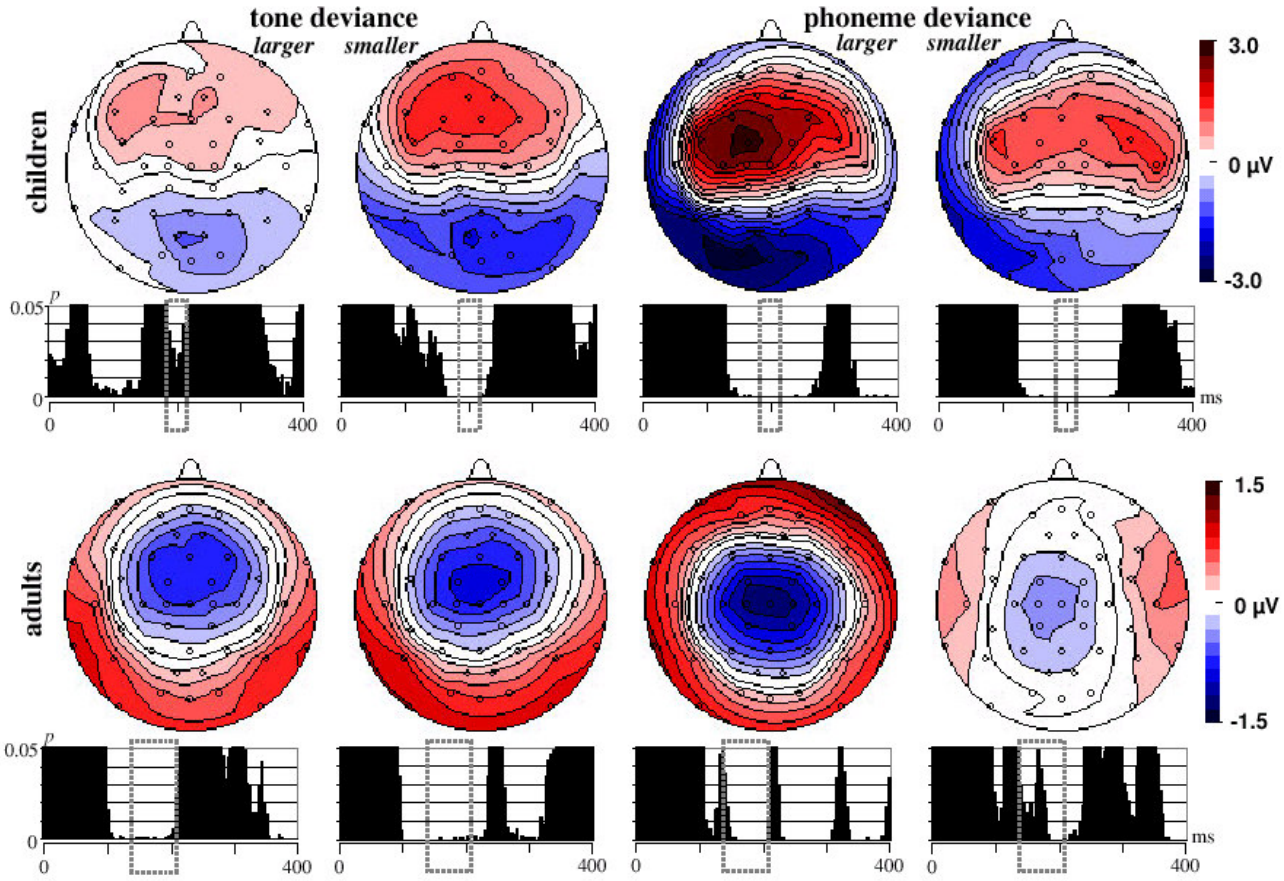

Fig. 5. Difference mismatch potential maps and point-to-point significance values of the mismatch response computed with the bootstrapping TANOVA. Low values at a certain time point indicate that standard and deviant maps are different (significant if $p < 0.05$, see scale). The continuous and consistent mismatch response periods are indicated by grey dotted boxes in the TANOVA plots. The difference maps are averaged over these periods. Frontally positive mismatch response in children (upper row, 179-207 ms), frontocentral mismatch negativity in adults (lower row, 129-199 ms). Frequency mismatch on the left (1st column: 1000 vs. 1060 Hz, 2nd column: 1000 vs. 1030 Hz), phoneme mismatch on the right (3rd column: ba vs. ta, 4th column: ba vs. da). Note the different amplitude scales (+/- 3µV for children and +/- 1.5µV for adults) indicating that children's mismatch potentials are about twice as large as in adults.

LORETA source localisation of these mismatch periods located the local maxima for both conditions and age groups in superior temporal regions (Fig. 6). The local LORETA maximum of the phoneme condition in adults (x = -59, y = -46, z = 8) was located 7 mm lower and 21 mm more posterior than that of children (x = -59, y = -25, z = 15), but the activated voxels showed a large overlap in the left temporal cortex. The local LORETA maximum of the tone condition in adults (x = 60, y = -32, z = 1) was located 7 mm lower than that of the children (x = -59, y = -32, z = 8), but in the right hemisphere. Adults' MMN sources were located bilateral for tones and left

lateralised for phonemes. Children's sources of the positive mismatch response were left lateralised for both stimulus types.

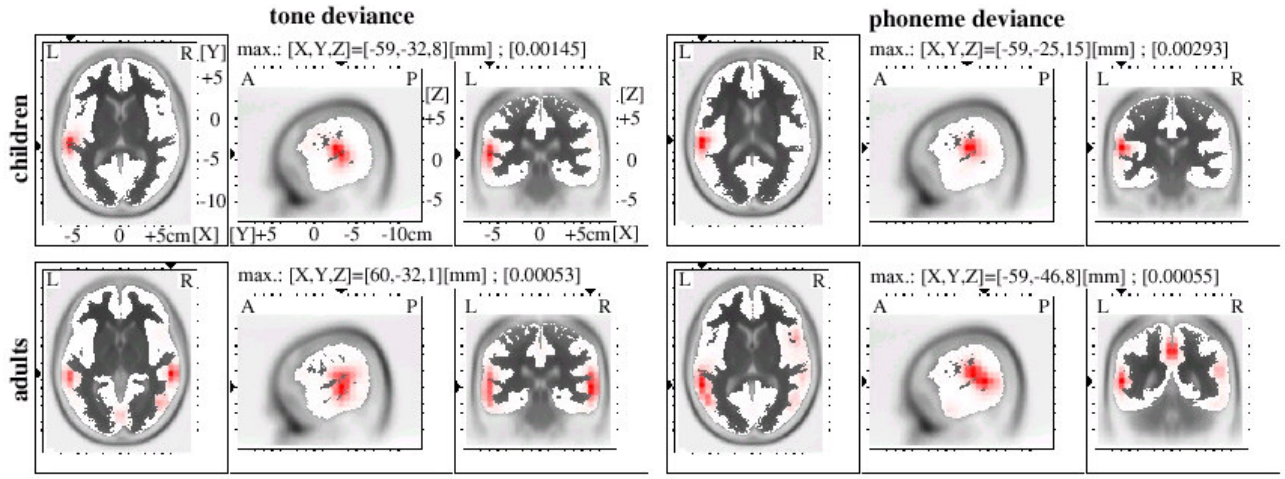

Fig. 6. LORETA sources of averaged mismatch potential maps for children (upper row) and adults (lower row), tones (on the left) and phonemes (on the right). Grandmeans of the 2 deviant mismatch responses were averaged. Sources were found at similar temporal locations in children and adults, but predominantely in the left hemisphere in children (L: left, R: right, A: anterior, P: posterior, max.: maximal LORETA value in Talairach space, indicated also with black triangles).

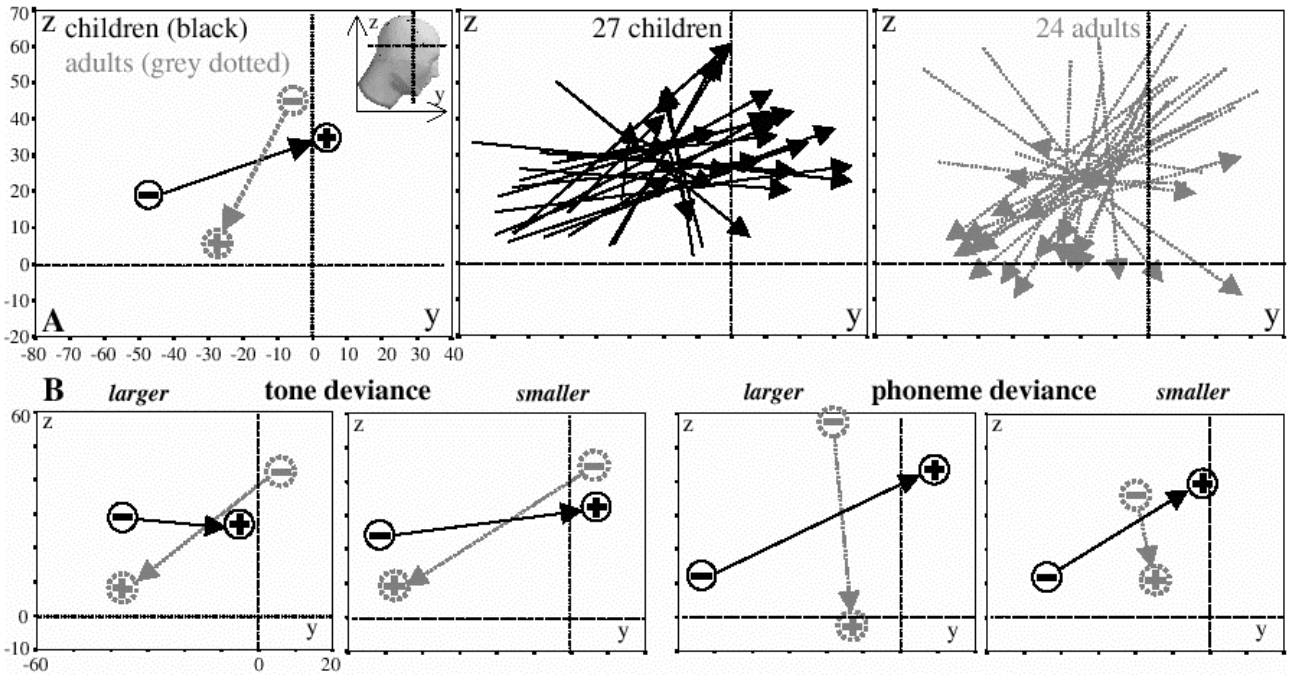

Fig. 7. Centroid distribution in children (black) and adults (grey dotted) of the averaged mismatch potential maps across all conditions plotted in Talairach space (A left). Children show a partial polarity reversal compared to adults, which is true for most of the individual cases (A middle and right). The polarity reversal is more pronounced for tones (B left half) than for phonemes (B right half).

As illustrated in table 3, children and adults differed in mean centroid location (*age group*) and in centroid distribution (*age group x polarity*). This latter effect reflected a partial reversal of positivity and negativity between children and adults. The polarity reversal was more complete for tones than phonemes (*age group x stimulus type x polarity*), and was also modulated by the level of deviance (*age group x stimulus type x deviance x polarity*). The GFP analyses (table 3) indicated that the mismatch response was stronger in children than in adults (*age group*). Mismatch response strength (GFP) was similar for phonemes and tones in adults but stronger for phonemes than for tones in children (*age group x stimulus type*), particularly for the larger deviance (*age group x stimulus type x deviance*).

Table 3. Effects on mismatch response strength and topography

Effect	Strength (GFP)	Topography				
		Centroid mean location		Centroid distribution		
		Multivariate	Axis	Polarity (***P***) interaction	Multivariate	Axis
Polarity (***P***)	**---**	**---**	-	***P***	(F(3,47) = 5.88 **	Y, Z
Age group (***G***)	F(1,49) = 173.1 ***	F(3,47) = 3.76 *	Y	***G x P***	F(3,47) = 28.70 ***	Y, Z
Stimulus condition (***S***)	F(1,49) = 24.2 ***	ns	-	***S x P***	F(3,47) = 6.39 **	Y
Deviance (***D***)	F(1,49) = 10.6 **	ns	-	***D x P***	F(3,47) = 3.59 *	X, Z
G x S	F(1,49) = 21.4 ***	ns	-	***G x S x P***	F(3,47) = 3.55 *	Y, Z
G x D	ns	ns	-	***G x D x P***	ns	-
S x D	F(1,49) =27.4 ***	F(3,47) = 2.85 *	X	***S x D x P***	ns	-
G x S x D	F(1,49) = 5.1 *	ns	**-**	***G x S x D x P***	F(3,47) = 4.49 **	Y, Z

* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$; X, Y, Z = univariate significant axis.

In addition (table 3), different centroid distributions were found for tones and phonemes (*stimulus type x polarity*), for larger compared to smaller deviance (*deviance x polarity*), and for their interaction (*stimulus type x deviance*). Positive and negative centroids also had different mean locations (*polarity*). GFP indicated that mismatch response strength increased with the degree of deviance (*deviance*). This increase of mismatch response strength with larger deviance was prominent for phonemes, while larger tone deviance elicited even somewhat weaker mismatch responses than small tone deviance (*stimulus type x deviance).*

Post hoc analysis revealed that for children's mismatch response maps, the negative centroids were posterior and inferior to the positive centroids, whereas for adults, the negativity was anterior and superior to the positivity (Fig. 7A left). This is listed in Table 3, where "*G x P"* indicates a multivariate significant "*age group x polarity*"-interaction, which was significant at the univariate level for the anterior-posterior and superior-inferior Talairach-dimensions (*y- and z-axes).* As is illustrated in Fig. 5, adults showed a typical MMN with frontocentral negativity and bilateral mastoid / temporal positivity. In contrast, children showed a reversed topography with anterior positivity and posterior negativity (Fig. 5). In addition to this polarity reversal, children's centroids were located generally more posterior than adults' centroids (Table 3, *G, y-axis*). The polarity reversal in children compared to adults was more pronounced for tones than for phonemes along the anterior-posterior axis (Table 3, *G x S x P*, *y-axis;* Fig. 7B left half), but more pronounced for phonemes than tones on the z-axis (Table 3, *G x S x P*, *z-axis;* Fig. 7B right half). As illustrated in Figure 1, this indicates that in both age groups the frontocentral pole of the mismatch response in the tone compared to the phoneme condition was located more anterior and inferior, and the mastoid/temporal pole more posterior and superior, with the polarities always reversed in children compared to adults. However, the phoneme mismatch responses of adults showed more concentric maps (Fig. 5) with more pronounced superior-infererior centroid orientation than all other conditions (Fig. 7). The age-related differences in centroid distribution were less pronounced for larger frequency and for smaller phoneme mismatch than for the other conditions (Table 3,

G x S x D x P, *y-axis and z-axis*). The lateralisation (x-axis) of the centroids did not vary with age group, but depended on stimulus type and deviance (*stimulus type x deviance, deviance x polarity*).

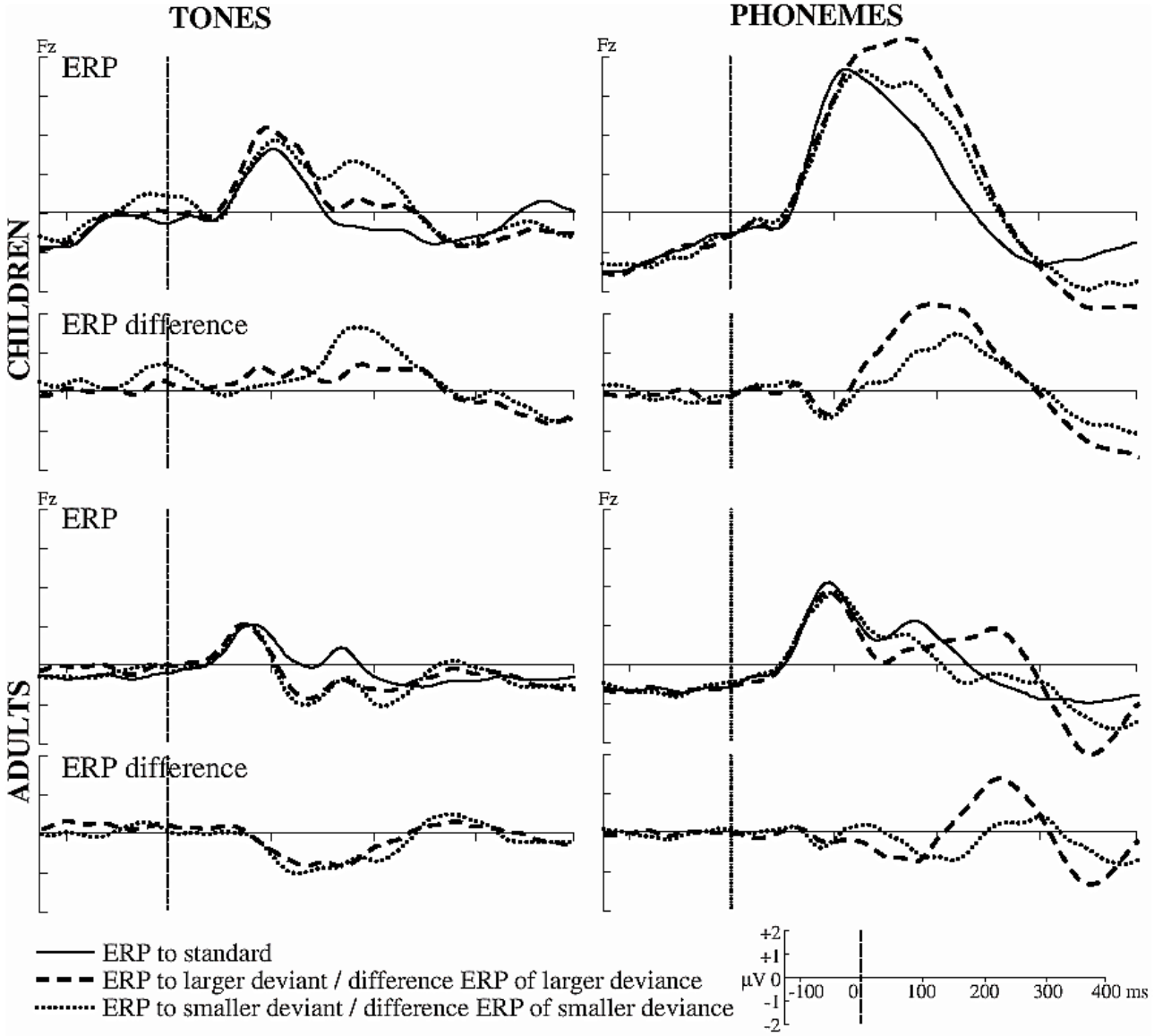

Fig. 8. ERP Waveshapes and ERP difference waves at Fz to tone (on the left) and phoneme stimuli (on the right) for children (upper two rows) and adults (lower two rows). Standards (solid line), larger deviants/larger deviance (dashed line) and smaller deviants/deviance (dotted line). The deviant waveshapes show a positive deflection in children and a negative one in adults after the initial positive peak.

The waveshapes to standards and deviants at Fz, which resulted in a frontal positive mismatch response in children but in an MMN in adults, are illustrated in Fig. 8. All stimuli in both age groups elicited an initial positivity (P1) between 50 and 100ms, and a smaller late negativity (N2) after 300ms. The frontal waveshape component sequence of adults consisted of an early P1 and a late N2, less pronounced

were the N1 and P2 components between. The waveforms to deviants showed a negative shift compared to standards starting after the initial P1 component. The ta-phoneme deviant (aspirated in german language) showed an additional prominent positive deflection after the MMN. Children's component sequence showed a large positive (P100) component followed by a negative component (N300). In the tone condition the deviants showed a larger P100 followed by a second positive shift after the P100. In the phoneme condition the positive shift of the deviants started at the P100 peak lasting for another 150 ms. Signs of a frontal MMN (i.e. more frontal negativity to deviants than to standards) in children appeared only after 270-300ms, and became significant only after 360ms (Fig. 5).

3.4 Discussion

In this ERP mapping study we compared automatic auditory deviance processing between normal children (6-7 year old) and adults, using an MMN paradigm with shorter SOA and smaller deviance than most previous studies with children. A topographic analysis of variance (TANOVA) revealed that standard and deviant ERP maps were different in all conditions for both age groups in periods corresponding to the MMN time window. Comparing positive and negative centroid locations of these averaged periods indicated different distributions of the two poles in children and adults, which were further explored.

Positive centroids were higher and more anterior located than negative centroids in children, whereas in adults the opposite was true. Whereas the adults' centroid locations (negative high, positive low) corresponded to a typical MMN distribution (frontocentral negativity, temporal positivity), the children's mismatch distribution was inverted to a frontal positivity with a posterior negativity. This frontally positive mismatch response in children reflected consistent and highly significant automatic discrimination of auditory change during the conventional MMN time window. Like the MMN, it reflected additional or increased (rather than decreased) neural

activation to deviants compared to standards. Its functional properties also closely resembled the adult MMN, as both mismatch responses increased with the degree of phoneme deviance, but not with the degree of tone deviance.

To our knowledge a frontal mismatch positivity replacing the MMN in this time range has not been reported in studies with children at a similar age (Cheour et al., 1997; Holopainen et al., 1997; Gomes et al., 1999; Kraus et al., 1999; Gomot et al., 2000; Shafer et al., 2000; Korpilahti et al., 2001; Cheour et al., 2002). All these studies used longer SOAs (>= 450 ms) and larger frequency deviance (>=10 %) than the present study (SOA: 383 ms, larger deviance: 6 %, smaller deviance: 3%). However, an inspection of the MMN illustrations in those studies reveals that positive mismatch responses often preceded, followed or even replaced the MMN in some conditions, but were not further discussed (Holopainen et al., 1997; Gomes et al., 1999; Gomot et al., 2000; Shafer et al., 2000; Korpilahti et al., 2001; Cheour et al., 2002). Whereas the frontal positivities following the MMN might be attributed to a P3a-like component (Squires et al., 1975, Gumenyuk et al., 2001), those preceding the MMN might be related to the positive mismatch response reported in the present study. Particularly, in three studies with phoneme or word deviance these positivities occurred at similar latencies as in the present study: In the study of Cheour et al. (2002), which investigated MMN to French vowels in Finnish children, a positivity (100-280 ms) was found in one measurement of one group instead of an MMN. In the doctoral thesis of Korpilahti (1996, unpub.) contrasting Finnish words, the children showed a prominent positivity (190-270) ms preceding the analyzed MMN. Using the same word stimuli with 5.7 year olds, Korpilahti et al. (2001) showed figures with a positivity (200-300 ms) after a small negativity and preceding a large negativity. For a pseudoword contrast their figures showed no MMN, but two positivities (150-200, 250-600 ms; Korpilahti et al., 2001). In conclusion, some studies using speech contrast showed figures with frontocentral positivities similar to that of the present study, while studies with frequency contrast used larger deviance than the present study, but occasionally showed figures with positive mismatch responses. Thus, in addition to short SOAs, a speech contrast and/ or a small deviance which is hard to

discriminate might be a prerequisite for the observed positive mismatch response at this age. This is supported by the behavioral discrimination results of the present study, where children had more difficulties discriminating the deviants than adults. We believe that this positive mismatch response to small deviance at short intervals should be distinguished from the P3a type positivities reflecting distractibility or involuntary attention to large deviance, and which are particularly prominent in infants or when using novel sounds as deviants. Support comes from a study of infants which reported that only a positive mismatch response was obtained with a small frequency deviance, while an MMN preceeded a positive mismatch response to large frequency deviance in children up to 12 months (Morr et al., 2002). Similarly, a recent study of infants and 2-year olds reported that an MMN was followed by a P3a like positivity to large frequency deviance (750 vs 500 Hz); for novels (with even larger deviance) this P3a completely replaced the MMN in 2-year olds (Kushnerenko et al., 2002). The authors suggest that the relatively large deviance used in their paradigms may have caused involuntary orienting. Indeed, the lack of a challenging visual foreground task in infant studies may even enhance such attentional effects. In contrast, the children in the present study were engaged watching video or playing gameboy and the deviances used were very small in order to minimize involuntary orienting. Consistent with this, there were no significant correlations between the widely used CBCL attention problem scale and the positive mismatch response (at Fz: larger tone deviance: $r = 0.29$, smaller tone deviance: $r = 0.29$, larger phoneme deviance: $r = -0.20$, smaller phoneme deviance: $r = -0.32$). The lack of significant (or even consistent) correlations suggests that the mismatch response found in the present study is not related to distractibility or involuntary orienting.

LORETA sources of the mismatch response were at similar superior temporal plane locations in children and adults, consistent with previous source localisation studies and with results from intracranial recordings in adults (Kropotov et al., 1995) as well as children (Liasis et al., 1999). The centroid distributions and sources for tone and phoneme mismatch differed only in adults. Adults' phoneme MMNs had a more pronounced superior-infererior centroid orientation than the tone MMNs, and

the sources were located bilateral for tones but left lateralised for phonemes, which is in accordance with earlier results (Alho, 1995; Näätänen, 2001a). The additional midline source in adults' phoneme MMN may indicate some attentional component, consistent with the P3a like activity following the phoneme MMN. In children the sources were left lateralised for both stimulus types. This may reflect different functional properties of the mismatch generators in children compared to the MMN generators in adults. Hovewer, the LORETA results regarding lateralisation should be considered with caution, since there were no significant effects on centroid lateralisation involving age group.

Similar LORETA source localisation, but opposite map polarity and centroid distribution thus characterised the initial automatic mismatch response in the two age groups. This suggests that the adults' frontocentral MMN and the children's frontally positive mismatch response originated from opposite surface polarity of similar generator structures in the superior temporal plane. In principle, a frontally positive mismatch response in children could also arise from surface negativity in a nearby cortical surface with opposite orientation above or below the Sylvian fissure. However, such structures have not been implicated in automatic auditory change detection, and intracranial recordings in these regions have identified focal mismatch activity confined to superior temporal structures in both children and adults. Our results thus demonstrate that the initial detection of small auditory change at short intervals activates qualitatively different neurophysiological mechanisms in the superior temporal planes of children and adults. This qualitative developmental difference appears limited to automatic auditory change detection, since similar frontocentral P1 topographies were observed in both age groups. For clinical MMN applications in children our results also have important implications. Such age-appropriate positive frontal mismatch responses reflect automatic mismatch detection. This should not be interpreted as a reduction or absence of MMN. A positive frontal mismatch response must also be distinguished from an absent MMN at the individual level. The two findings have different interpretations (strong but possibly immature vs. weak auditory memory trace) with distinct clinical

implications. The developmental trajectory must involve a reduction of this large frontocentral positive mismatch response for the smaller adult MMN to emerge. Whether the frontal positive mismatch response undergoes a genuine polarity reversal, or whether it disappears, and either gets replaced by the late frontal MMN decreasing in latency (from over 370ms) or unmasks a 'typical MMN", is unclear. As critical individual transitions may be masked in cross-sectional studies, our longitudinal study with a planned follow-up of these children at age 8 with a focus on individual developmental changes should shed light on these issues.

4. Altered responses to tone and phoneme mismatch in kindergartners at familial dyslexia-risk [3]

4.1 Introduction

Developmental dyslexia is a common learning disorder with a substantial genetic or familial background (Pennington and Lefly, 2001). Dyslexia is characterised by a phonological processing deficit (Liberman et al., 1974; Torgesen et al., 1994; MacDonald and Cornwall, 1995), possibly due to a deficit in more general auditory processing (Tallal, 1980). Markers of these deficits might help concerned families to seek early training or provide relief. The mismatch negativity (MMN, 100-250ms), an automatic event related potential (ERP) response to auditory deviance (Näätänen et al., 1978), and a subsequent similar late negativity (late MMN, 300-600ms; Korpilahti et al., 1995), might be such markers. Sources of the MMN to deviance in basic acoustic sound features have been located mainly in the bilateral auditory cortex with some evidence for additional frontal sources (Alho, 1995), whereas MMN to speech sound deviance seems to origin mainly from left temporal sources (Näätänen, 2001b). The MMN is developmentally quite stable and can be elicited in children although with slightly longer latencies (Cheour et al., 2000). However, we recently showed that this (early) MMN can be replaced by a frontally positive mismatch response (MMR) in kindergarten children when using small deviance and short intervals (Maurer et al., 2003). Similarly, in infants the MMN can be replaced by a frontally positive mismatch response, which has been reported to be even larger in newborns with a familial risk for dyslexia compared to controls in a phoneme MMN paradigm (Leppänen et al., 1999). In 6 month old infants in addition to a larger positive mismatch response the subsequent MMN like negativity was attenuated over the left hemisphere (Leppänen et al., 2002). However, there are no such studies

[3] *to be submitted to Neuroreport*

investigating mismatch response differences between groups with and without risk in older preschool children, i. e. at an age when early training in order to prevent dyslexia would be most promising. MMN was investigated only later after dyslexia already had been developed. In dyslexic adults compared to controls MMN area was attenuated to small frequency deviance, whereas no difference was reported to duration deviance (Baldeweg et al., 1999). In contrast in another study, using larger frequency deviance neither MMN nor late MMN were attenuated in dyslexic adults, whereas the late MMN to phoneme deviance was attenuated (Schulte-Körne et al., 2001). Similarly, reduced late phoneme MMN was obtained in dyslexic school children but no differences in frequency MMN using smaller deviance (Schulte-Körne et al., 1998). These differences in late phoneme MMN might be related to attenuated late MMN to complex tone pattern deviance as two studies suggest (Schulte-Körne et al., 1999; Kujala et al., 2000). Different MMN topographies have not been reported or investigated in any of these studies except for a more posterior located MMN to tone pattern deviance followed by a less right side late MMN preponderance in dyslexic subjects (Kujala et al., 2000).

In conclusion, different MMN or late MMN between dyslexic subjects and controls have been reported for phoneme and tone pattern deviance, and less consistently for frequency deviance. Such differences seem not only to exist between dyslexic subjects and controls, but also between subjects with and without familial risk for dyslexia. However, the latter differences were only investigated in infants and not with older children. In addition to the traditional MMN amplitude analysis at mid-frontal electrode site, a more topographically oriented approach might be promising in detecting additional risk group differences.

Table 4. Risk and control groups with parents‘ reading measures

			risk group		control group	*p* (*t*-test or Chi-square)	risk group	control group	*p* (*t*-test or Chi-square)
			initial n = 32	consistent n = 31	n = 29		matched n = 28	matched n = 28	
age (years)			6.64 (± 0.32)	6.64 (± 0.32)	6.49 (± 0.38)	< 0.1	6.60 (± 0.30)	6.50 (± 0.37)	>0.3
sex (male : female)			17 : 15	17 : 14	15 : 14	> 0.7	14 : 14	14 : 14	= 1
handedness (right: left)			29 : 3	28 : 3	25 : 4	> 0.5	25 : 3	24 : 4	> 0.5
IQ			103.3 (± 9.5)	103.4 (± 9.7)	107.6 (± 13.3)	< 0.2	103.8 (± 9.7)	107.4 (± 13.5)	>0.25
phonological risk			2.5 (± 1.9)	2.5 (± 1.9)	1.7 (± 1.3)	< 0.1	2.6 (± 2.0)	1.6 (± 1.0)	<0.05
parents	ARHQ	affected	.48 (± .13)	.48 (± .14)		<0.001	.49 (± .14)		<0.001
		unaffected	.27 (± .11)	.27 (± .11)	.28 (± .12)	ns	.26 (± .10)	.28 (± .13)	ns
	stories (time):	affected	138.4 (± 46.5)	139.6 (± 46.9)		<0.01	139.5 (± 49.6)		<0.01
		unaffected	109.5 (± 12.8)	109.5 (± 12.8)	108.4 (± 16.9)	ns	108.0 (± 12.7)	108.5 (± 17.2)	ns
	stories (errors):	affected	8.9 (± 8.6)	9.2 (± 8.6)		<0.001	8.5 (± 7.3)		<0.001
		unaffected	3.4 (± 2.6)	3.4 (± 2.6)	2.7 (± 2.3)	ns	3.6 (± 2.7)	2.7 (± 2.4)	ns
	pseudowords (time):	affected	63.9 (± 18.0)	64.7 (± 17.9)		<0.001	64.8 (± 18.6)		<0.001
		unaffected	45.1(± 5.7)	45.1 (± 5.7)	46.8 (± 10.3)	ns/	44.9 (± 6.0)	46.7 (± 10.4)	ns/
	pseudowords (errors):	affected	2.6 (± 2.6)	2.7 (± 2.6)		/ < 0.05	2.6 (± 2.6)		< 0.1
		unaffected	1.4 (± 0.7)	1.4 (± 0.7)	1.5 (± 1.5)	ns	1.4 (± 0.7)	1.5 (± 1.6)	ns

4.2 Materials and Methods

Thirty-two kindergarten children with a familial risk for dyslexia (with at least one first grade relative reporting dyslexia) and 29 control children participated in this study (table 4). All families provided informed consent and the children received a present for their participation. All children had normal intelligence (IQ>85), normal visual and auditory acuity, and all families had a (Swiss) German background. All children were tested for intelligence (CFT-1; Weiss and Osterland, 1997), phonological abilities (BISC; Jansen et al., 1999), and letter and word reading knowledge. All parents filled out the child behaviour checklist (CBCL; Achenbach and Edelbrock, 1983) and a reading history questionnaire (ARHQ; Lefly and Pennington, 2000). To corroborate the self-reported dyslexia affected parents and older siblings were tested with story and pseudoword reading tests. Thirty parents from the control group and 9 unaffected parents from the risk group also performed the reading tests. One child from the risk group was excluded because the parent reporting dyslexia had a normal ARHQ-score (<0.40) and both reading scores were within 1 SD of the control parents' mean, indicating good reading abilities and no history of reading problems. No control child had to be excluded because of parents having high ARHQ-scores as these parents had normal reading scores (within 1SD) in at least one test. The final groups (31 children at risk, 29 control children, see table 4) did not differ regarding intelligence, sex and handedness. However children at risk tended to be older and more impaired in phonological processing than controls. Thus, the critical group effects were additionally tested with groups matched for age, IQ, handedness, and sex (table 4), and changes in significance are reported.

Frequency and phoneme stimuli were presented in separate MMN experiments. The auditory frequency stimuli consisted of one standard (1000 Hz) and two deviant tones (larger deviant: 1060 Hz, smaller deviant: 1030 Hz). The phoneme stimuli were naturally spoken and also consisted of one standard ("ba") and two deviants (larger deviant: "ta", smaller deviant: "da"). The stimuli were 100 ms in duration (including 5 ms rise and fall times) and were presented binaurally by speakers at 78dB at a rapid

rate (stimulus onset asynchrony: SOA=383ms). Stimulus order was pseudo-randomized with not less than two standards between two deviants. The percentage of each deviant was 8.33 % (1500 standards, 150 larger deviants, 150 smaller deviants). Children sat quietly and ignored the stimuli watching videos or playing Gameboy. All games or videos were either silent or set to a low sound level.

Behavioural discrimination of the same stimuli was tested about 10 days before the electroencephalography (EEG) recording. 80 trials consisting of 6 stimuli were presented in separate runs for tones and phonemes. All stimuli of a trial were standards except the 4^{th} stimulus which could be a standard (50%) or one of the two deviants (25% each). The within-trial SOA was the same as for the EEG experiment. Trials were separated by 800 ms. The subjects had to press a mouse button, whenever they perceived a deviant stimulus. Visual feedback (blue print = correct, red print = incorrect) was given after every response.

The 43 channel ERPs were recorded at 500 Hz/channel with filter settings 0.1-70 Hz and with calibrated technical zero baselines. Caps (Easy Cap, FMS, Munich) were used for the montage (10-20 system plus Fpz (recording reference), Oz, FT9/10, FC5/6, TP9/10, CP5/6, PO9/10, AF1/2, FC1/2, C1/2, CP1/2, PO1/2 and two EOG electrodes below the outer canthus of each eye). O1/2 and Fp1/2 were displaced 2 cm laterally for more even coverage. Impedance was kept below 20 kΩ. The continuous EEG was corrected for horizontal and vertical eye movements and in some cases for slow wave artefacts using an advanced method to minimise topographic EEG distortion (Berg and Scherg, 1994). Corrected EEGs were digitally lowpass filtered (30 Hz, 48 dB/oct), downsampled to 256 Hz, and segmented (-125 ms prior and 1000 ms following the stimulus). Trials with artefacts exceeding ±100 μV in any channel were automatically rejected before averaging. Averaging was done separately for standard and two deviants of each stimulus type.

The ERPs were transformed to the average reference (Lehmann and Skrandies, 1980) which was used for all subsequent analyses. Individual differences between the

two deviants and the standard (mismatch responses), and grand averages for standard, deviants and differences were computed.

To assess mismatch response periods, standard and deviant ERP maps of all 61 kindergarten children were first compared with a topographical bootstrapping approach. This TANOVA (topographic analysis of variance; Strik et al., 1998; Pascual-Marqui et al., 1999) computes the exact probability of dissimilarity between two maps (Lehmann and Skrandies, 1980) using bootstrapping statistics. For direct group comparison we selected the periods which exhibited continuous and consistent mismatch responses with significant differences for at least three successive time frames and all four deviants. Additionally, the MMR segment we reported in previous work was analysed (Maurer et al., 2003). All subsequent analyses were performed on the mismatch responses (difference maps: deviant-standard). After averaging the mismatch responses over these periods, Global Field Power (GFP) and 3D centroids (centre of gravity for positive and negative map regions) were computed at the individual level for each deviance and stimulus type separately (Brandeis et al., 1994). GFP is a measure for the electric field strength, whereas the 3D centroids represent the topography of the field. The 3D centroid locations were defined in Talairach coordinates (Talairach and Tournoux, 1988).

GFP, location of the 3D centroids, and Fz-amplitude (for comparison with previous work) were analysed in each mismatch response segment in three Multivariate Analyses of Variance (MANOVA) for repeated measures with the between subject factor "*risk*" (with vs. without risk) and within subject factors *" segment"* (early vs. late segment), "*stimulus type*" (tones vs. phonemes), "*deviance*" (larger vs. smaller) and "polarity" (positive vs. negative, centroid analysis only) . The 3 centroid location dimensions (x-, y-, and z-axis) were treated as multivariate dependent measures. Accuracy results from the behavioural discrimination task were transformed into *d'* sensitivity measures and analysed in a "*risk" x* "*stimulus type*" x "*deviance*" MANOVA for repeated measures. For all statistical tests only effects involving the "*risk"* factor are discussed. The significance level was set to 0.05, but trends ($p < 0.1$) of specific theoretical interest are also reported.

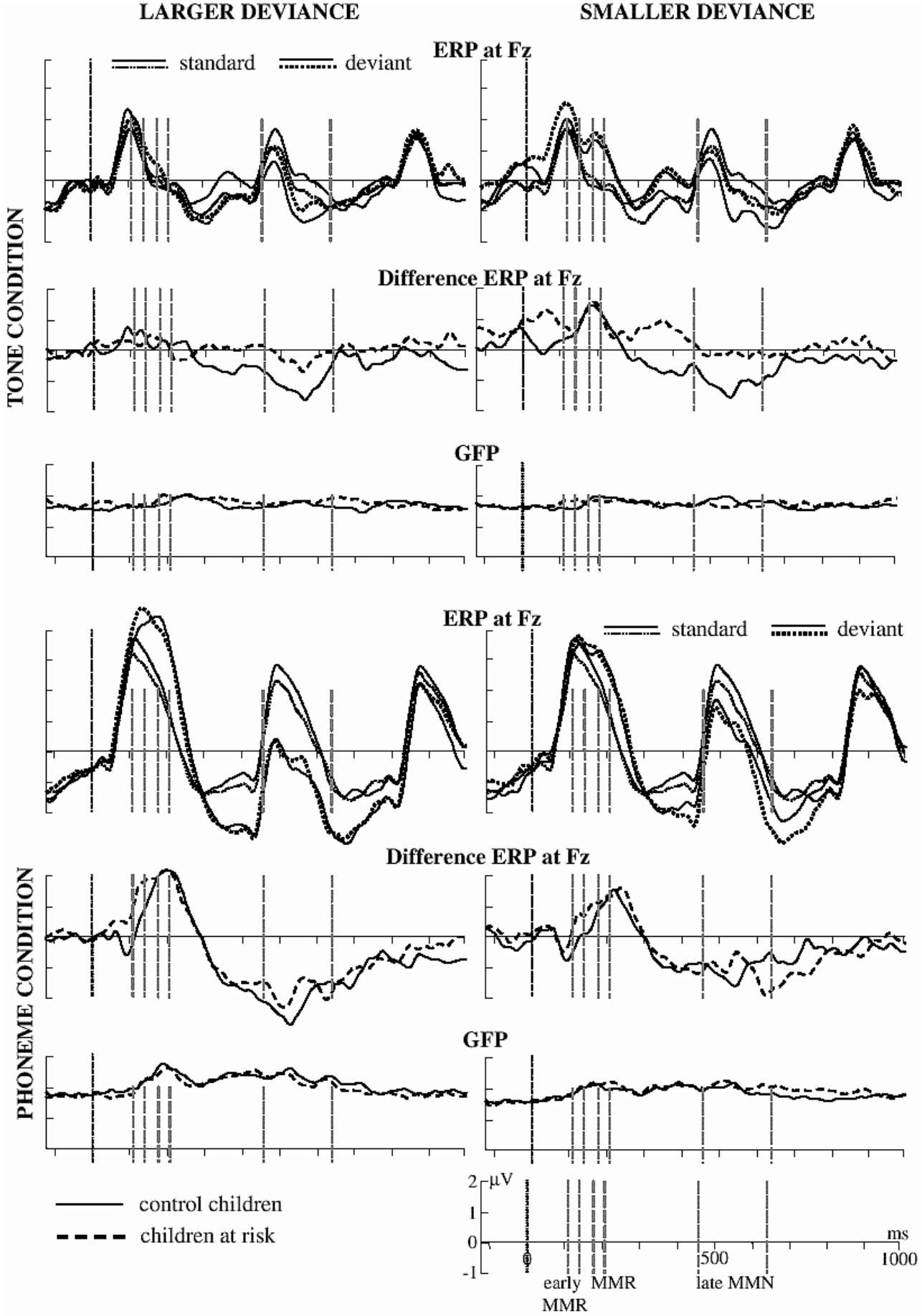
LARGER DEVIANCE
SMALLER DEVIANCE
ERP at Fz
standard
deviant
TONE CONDITION
Difference ERP at Fz
GFP
ERP at Fz
standard
deviant
Difference ERP at Fz
PHONEME CONDITION
GFP
control children
children at risk
2 μV
1
0
-1
ms
500
1000
early MMR
MMR
late MMN

Fig. 9 (previous page). ERPs to standards and deviants deviants (1st,4th row), difference waves (2nd, 5th row), and GFP (3rd, 6th row) for children at risk (dotted/dashed lines) and control children (solid lines). Mismatch segments are indicated by vertical dashed lines. Difference waves of the children at risk show more positive values in the early MMR segment in the phoneme condition and less negative values in the late MMN segment in the tone condition.

4.3 Results

Control children showed a trend towards better discrimination than children at risk (*d'* risk: 2.19, d' controls: 2.60, *risk*, $F(1,58) = 3.96$, $p < 0.1$). This trend became significant with matched groups (*risk*, $F(1,54) = 5.98$, $p < 0.05$), and tended to be more pronounced for phoneme discrimination (*risk x stimulus condition*, $F(1,54) = 3.86$, $p < 0.1$).

The periods during which standard and deviant ERP maps for all 4 conditions (2 stimulus types x 2 deviance levels) differed were between 109 and 140 ms (early frontocentrally positive mismatch response = early MMR) and between 457 and 636 ms (late MMN). The frontocentrally positive mismatch response between 179 and 207 ms (MMR) from our previous work (Maurer et al., 2003) was significant for both phonemes, but only for the smaller tone deviance.

For the early MMR the Fz-amplitude analysis revealed a trend for children at risk to have more positive values than control children (*risk,* $F(1,58) = 3.054$, $p < 0.1$). As can be seen in the difference waves in Fig. 9 this was mainly due to the phoneme condition, but this interaction only approached significance ($p < 0.11$; $p < 0.1$ with matched groups). Accordingly, *posthoc* tests for the stimulus conditions separately revealed a significantly larger positivity in children at risk only for the phoneme condition ($p < 0.05$). Testing the four deviances separately revealed significant group differences only for the larger phoneme deviance ($p < 0.05$). No group effects were found in the GFP and centroid analyses of the early MMR segment.

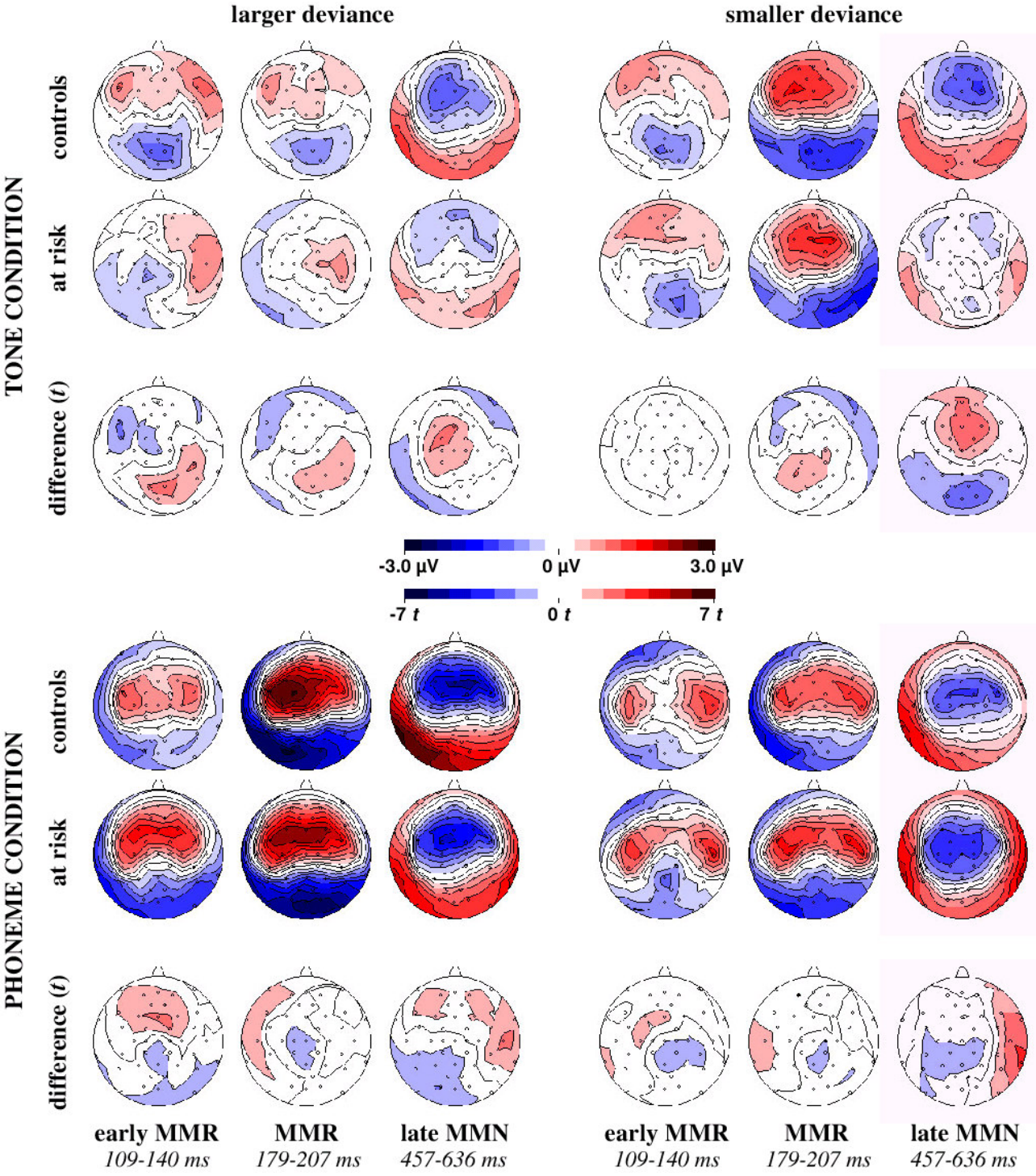

Fig. 10. Voltage and *t*-maps of the averaged mismatch response periods (early MMR, 109-140 ms; MMR, 179-207 ms; late MMN, 457-636 ms) for children at risk (2nd, 5th row), control children (1st, 4th row), and their difference (3rd, 6th row). Maps of the tone condition are in the upper half, those of the phoneme condition in the lower half. Maps of the larger deviance on the left, maps of the smaller deviance on the right. The early MMR and the MMR have a partially reversed polarity compared to the late MMN. In children at risk the late tone MMN is attenuated and the late phoneme MMN shows two positive poles in contrast to only one left lateralised pole in control children. Accordingly, *t*-maps indicate that children at risk mainly show less frontocentral negativity in the late tone MMN and less positivity at right temporal sites in the late phoneme MMN.

For the subsequent MMR segment from our previous work (Maurer et al., 2003) no significant group differences were found in the Fz-amplitude and centroid analyses. However, for GFP there was a significant 3-way group interaction (*risk x stimulus condition x deviance*, $F(1,58) = 4.75$, $p < 0.05$): both groups had more GFP to the larger deviance than to the smaller deviance in the phoneme condition, but in the tone condition this was only true for the children at risk, whereas the control children had less GFP to the larger frequency deviance than to the smaller one. However, *posthoc* tests for the stimulus conditions separately revealed only a trend for a *risk x deviance* interaction in the tone condition ($p<0.1$), and no significant group differences for any of the four deviances (all *ns*).

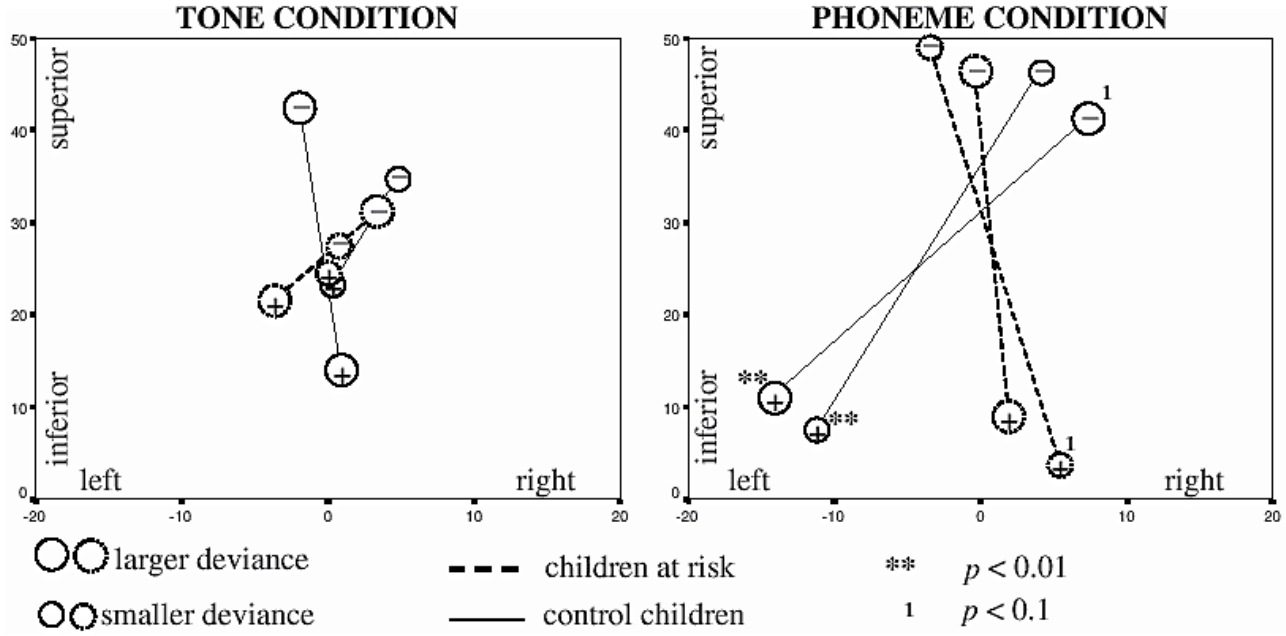

Fig. 11. Positive and negative centroids for frequency deviance (left) and phoneme deviance (right). In the phoneme condition the positive centroids are strongly left lateralised in control children for larger (larger circle) and smaller deviance (smaller circle), and located near midline or slightly right lateralised in children at risk (dotted circles). No such left lateralisation can be seen in the tone condition, and the centroid locations show less clear positions especially in children at risk due to the smaller late MMN compared to the phoneme condition. Significance values of lateralisation tests (*t*-tests against midline) are indicated in the figure.

In the late MMN segment the negativity at mid-frontal electrode site Fz was attenuated in children at risk compared to control children (*risk*, $F(1,58) = 5.19$, $p < 0.05$). Post hoc tests revealed a significant late MMN attenuation in children at risk only in the tone condition ($p < 0.01$), but not in the phoneme condition ($p > 0.5$).

However, the *stimulus condition x risk group* interaction only approached a trend ($F(1,58) = 2.70$, $p < 0.11$). A GFP-interaction with risk group (*stimulus condition x deviance x risk,* $F(1,58) = 5.82$, $p < 0.05$; $F(1,54) = 3.52$, $p < 0.1$ with matched groups) was also found: Whereas in the phoneme condition both groups had larger GFP to the larger deviance than to the smaller deviance, in the tone condition this was only true for the risk group, but not for the control group, where GFP was larger to the smaller deviance than to the larger deviance. Separate *posthoc* group comparisons for all four deviances were all not significant.

The late MMN map topographies also differed between the groups (Fig. 10): centroid distribution was different between children at risk and control children (*risk x polarity,* $F(3,56) = 3.69$, $p < 0.05$). The positive centroids were located more left posterior and the negative centroids more right anterior in control children, whereas both centroids were located near the midline with a less pronounced anterior-posterior difference in children at risk (x- and y-axis). The centroid distribution difference between the two groups was modulated by the stimulus condition (*risk x stimulus condition x polarity,* $F(3,56) = 5.22$, $p < 0.01$), indicating that the groups differed in lateralisation to phoneme deviance. This was also reflected by different centroid mean location between children at risk and control children (*stimulus condition x risk,* $F(3,56) = 3.22$, $p < 0.05$; $F(3,52) = 2.72$, $p < 0.1$ with matched groups). As can be seen in Fig. 11, whereas in both groups, positive and negative centroids to tone deviance were located near the midline, the positive centroids to phoneme deviance were strongly left lateralised in control children, which was not true in children at risk (Fig. 11, x-axis). Lateralisation tests against the midline confirmed the left lateralisation of the two positive phoneme centroids in control children (both $p < 0.01$; see Fig. 11), and revealed no significant lateralisation in the tone condition or in children at risk. As indicated in Fig. 2 (voltage and *t*-maps) this lateralisation difference was rather due to larger positive values at right temporal sites than to less positive values at left temporal sites. The topographic differences on the z-axis were mainly due to differences in the tone condition: whereas in control children positive centroids were clearly below the negative centroids for both tones

and phonemes, in children at risk this inferior-superior centroid distribution was only pronounced for phonemes (Fig. 11, y-axis). Fz-amplitude and left-right positive centroid lateralisation of the early MMR was significantly correlated with the MMR (r between 0.34 and 0.59), but not significantly with the late MMN in all four deviances (r between 0.07 and 0.20). In contrast, GFP of the early MMR was significantly correlated with both MMR (r between 0.40 and 0.70) and late MMN (r between 0.26 and 0.75) in all four deviances.

4.4 Discussion

Kindergarten children with and without risk for dyslexia produced significant mismatch responses in both an early MMR segment and a late MMN segment. In the early MMR segment children at risk had similar GFP and topography as controls, but tended to have a larger positivity at mid-frontal electrode site (Fz), especially for phonemes. Remarkably, a similar enhancement of a positive mismatch response to phoneme deviance has been reported for infants at a dyslexic risk (Leppänen et al., 1999; Leppänen et al., 2002). However, no amplitude differences at Fz between the risk groups were found in the subsequent MMR, a mismatch response segment from our previous work, where we compared only the control children with adults (Maurer et al., 2003). This suggests that the focal risk group effects at Fz were limited to the onset of the frontocentrally positive mismatch response (early MMR).

In contrast to these minor differences in the early positivity segment, clear group differences were found in the late MMN segment, where we detected an attenuated late MMN and a different late phoneme MMN topography in children at risk. The late MMN was attenuated across both stimulus conditions and was especially pronounced in the frequency condition as *posthoc* tests revealed. This is in line with the results of Baldeweg et al. (1999) reporting an attenuated frequency MMN in dyslexics, but contrasts with the results of Schulte-Körne et al. (1998; 2001) reporting no differences between dyslexics and controls for frequency deviance. The reason for

those discrepancies is unknown. Our results support the hypothesis of a basic auditory processing deficit in dyslexia. The fast presentation rate in the present study might play an important role for the occurrence of the frequency MMN attenuation in the children at risk, in accordance with a deficit in temporal auditory processing (Tallal et al., 1996).

In two studies of Schulte-Körne (Schulte-Körne et al., 1998; Schulte-Körne et al., 2001) the late MMN to phoneme deviance was attenuated in spelling disabled subjects. In contrast, in our results the differences in the late phoneme MMN were not found in amplitude, but in topography. Control children had a left lateralised positive pole of the late phoneme MMN, whereas children at risk had a bilaterally symmetric late phoneme MMN. The topographical ERP methodology used, is especially suited to detect such topographical differences and emphasized the strong left-lateralisation of the mastoid positivity over the light right-shift of the frontal negativity. The strongly left lateralised gradients of the late phoneme MMN in control children suggests sources predominantly located in the left auditory cortex in contrast to bilateral sources in children at risk. The larger *t*-values of the between group difference maps at right than left temporal sites suggest rather an additional involvement of the right hemisphere in children at risk in automatic phoneme processing than a reduced activation of the left hemisphere. Interestingly, children at risk with better scores in a rhyming test had more left lateralised positive centroids of their late phoneme MMN ($r = -0.56$). In controls such a strong correlation was absent ($r = 0.15$). These results are consistent with a phonological core deficit causing dyslexia (Torgesen et al., 1994) and with earlier results regarding lateralisation differences in anatomy (Galaburda et al., 1994) or function Helenius et al., 2002) of the auditory cortex between dyslexics and controls and even in infants at risk (Leppänen et al., 2002). Additional support for the phonological deficit theory comes from the behavioural results, where children at risk showed a trend to a worse discrimination of phonemes.

4.5 Conclusion

The differences between children with and without familial risk for dyslexia in automatic auditory processing of both frequency and phoneme deviance suggest that these ERP features mainly reflect trait markers. Alternatively, this might indicate processing deficits in a large part of the children at risk, which are too subtle to interfere with learning to read and thus not lead to the clinical symptoms of dyslexia. If these differences are even larger in those children who will later develop a dyslexia and thus might be used as early markers, will be answered in a follow-up study with the same children after learning to read.

5. General Discussion

5.1 Learning to read

One of the three experimental studies investigated implicit visual word and form processing in kindergarten children and adults using a repetition detection task. In contrast to the other two studies about automatic auditory processing, children who could already read words were excluded from analysis in order to maximise the effect of literacy.

As expected, illiterate kindergarten children missed equally word and symbol targets, suggesting that a more efficient strategy for detecting word targets was not yet available. The adults in contrast, missed far fewer words than symbols, probably because their reading skills allowed them to code words more efficiently at lexical or semantic level.

To map the brain functions of word and symbol processing and determine the time frames, when words and symbols start to be processed differently, the ERPs of adults and children were divided in 7 segments and analysed regarding map strength (GFP) and topography. While GFP did not reflect word-symbol processing differences between the two age groups, topographic ERP measures detected such differences, both in the overall analysis and at the individual segment level.

In the N200 segment word and symbol maps were clearly different in adults (absolute and relative topography), but not (absolute topography) or only marginally (relative topography) different in children. The N200 component is thought to represent specialised and automatic processing of complex visual features such as faces or words (Allison et al., 1994; Bentin et al., 1999). This indicates that the kindergarten children have not yet developed specialised visual areas for word processing. However, the marginal negative differences found at occipito-temporal electrodes were similar to the adults' differences, although predominantely at the right hemisphere sites. Accordingly, this specialisation for words may already have

started to develop in these children. Interestingly the word-symbol difference at the right occipito-temporal electrode was larger in children with high letter knowledge than in children with low letter knowledge. This would be consistent with the notion that the VWF area might be built during learning to read under guidance of higher language functions, such as phonological processing (Cohen et al., 2002). However, despite these marginal word-symbol differences the large differences as recorded in adults must develop somewhere between kindergarten and adulthood, maybe even shortly after learning to read. Indeed, preliminary results from the same children at 2nd grade indicate that N200 topography for words (but not for symbols) has changed into two negative posterior poles as in adults and that N200 word-symbol difference increased dramatically.

With a spherical head model, LORETA localised the sources of the adults' N200 in the bilateral extrastriate visual cortex similar to source estimation of Michel et al. (2001). In contrast the visual word form area was mainly located in the left fusiform gyrus using ERP methods combined with fMRI (Cohen et al., 2000; Cohen et al., 2002) or MEG (Tarkiainen et al., 1999). The source localisation of the present data suggest that the N200 might not only be generated by sources in the left fusiform gyrus, but also by sources located more superior in the (bilateral) extrastriate visual cortex, to which, electrical measures may be more sensitive than magnetic or metabolic ones. Alternatively, sources in the fusiform gyrus might produce electric fields on the scalp which might be difficult for LORETA to correctly estimate within a spherical head model. This would be in agreement with the more left lateralised and more inferior located sources we got, when we used LORETA with a realistic head model.

Although the kindergarten children did not yet show the specialised early visual word processing, later segments of their ERPs indicated that they already discriminated between words and symbols. These word-symbol differences occurred in a later time range (after 400 ms) with a right posterior negative and left fronto-temporal positive ERP map topography. LORETA sources of these word maps were located in the posterior visual cortex and not in the anterior (temporal) language

areas. This might reflect a distinct visual precursor stage of word reading, and could suggest that implicit learning to read starts already before the actual formal training. Our world is full of letters, and children may become familiar with letters without knowing their names. Indeed, the results of an additional behavioural study with kindergarten children at 1st and 2nd level (5 and 6 year-olds) corroborated that visual letter recognition precedes letter naming. Five year-olds named 56 % of upper case letters (6 year-olds: 67 %), but already recognised 85 % of them visually as letters (6 year-olds: 91 %). Furthermore, only 37% of the children at 2nd Kindergarten level from the additional study, could read none or only one of the tested words, and thus would have reached the inclusion criterion of the ERP study. This may suggests that the kindergarten children in our ERP study are not representative in respect to their word reading abilities. However, the results also indicate that it is nearly impossible to find kindergarten children without any letter knowledge. Accordingly, the kindergarten children without word reading knowledge in the ERP study still named 11 upper case letters in average.

5.2 Development

In addition to these word and symbol processing differences between kindergarten children and adults, which presumably are related to reading ability, children had in general more GFP and different topographies than adults and their segment borders occured later than those of adults. This is in agreement with other developmental studies reporting longer latencies and larger amplitudes for children than for adults along with different topographies (Kok and Rooijakkers, 1985; Taylor and Smith, 1995; Taylor and Keenan, 1999). The longer latencies in children might reflect that their neurons are largely unmyelinated and thus conduct more slowly. Myelination of the neurons continues until adulthood and is crucial for fast signal transmission (Nelson and Monk, 2001; Sampaio and Truwit, 2001). Alternatively, the longer latencies in children might be due to less efficient processing, due to less developed

neural circuit and connections (Nelson and Monk, 2001). The increased amplitudes might also reflect less efficient processing using redundant synaptic connections. Changing topographies might be due to major changes in synaptic connectivity during development, with specialisation and recruitment of new neural networks (Nelson and Monk, 2001).

Similar to these general developmental differences in visual processing, children showed also large differences in automatic auditory processing compared to adults. This affected not only the evoked responses, but also differential responses reflecting automatic discrimination and sensory memory. The automatic mismatch response was stronger in children than in adults, especially for phonemes. This larger GFP might again be explained by less efficient automatic auditory processing in children with more neurons involved than in adults (Nelson and Monk, 2001). Latency differences between the age groups were not statistically tested, but grand means suggested also longer latencies of standard and deviant ERPs for children compared to adults. The most dramatic difference however between children and adults was a partial polarity reversal of the automatic mismatch response. Whereas adults showed a typical MMN with frontal negativity and temporal positivity, children's mismatch response was frontally positive. Such a positive mismatch response in a similar time range has not been reported in other studies investigating children at a similar age (Cheour et al., 1997; Holopainen et al., 1997; Gomes et al., 1999; Kraus et al., 1999; Gomot et al., 2000; Shafer et al., 2000; Korpilahti et al., 2001; Cheour et al., 2002). An explanation for this discrepancy might be that all these studies used longer intervals and larger frequency deviance than the present study.

However, a close inspection of the MMN illustrations in those studies revealed that positive mismatch responses often preceded, followed or even replaced the MMN in some conditions, but were not further discussed (Holopainen et al., 1997; Gomes et al., 1999; Gomot et al., 2000; Shafer et al., 2000; Korpilahti et al., 2001; Cheour et al., 2002). Whereas the frontal positivities following the MMN might be attributed to a P3a-like component (Squires et al., 1975, Gumenyuk et al., 2001), those preceding the MMN might be related to the positive mismatch response reported in the present

study. Particularly, in three studies with phoneme or word deviance these positivities occurred at similar latencies as in the present study (Korpilahti, 1996; Korpilahti et al., 2001; Cheour et al., 2002).

Thus, these illustrations suggest that in young children a frontocentrally positive mismatch response may precede or disturb the MMN. In addition, a fast presentation rate in combination with small frequency deviance or with speech deviance might enhance the occurrence of such a developmental difference in young children compared to adults.

This positive MMR to small deviance at short intervals should be distinguished from the P3a type positivities reflecting distractibility or involuntary attention to large deviance. P3a or novel P3 are frontally positive peaks at about 300 ms to deviant stimuli in passive auditory oddball paradigms, but they occur only, if the deviance is large or novel (Courchesne et al., 1975; Squires et al., 1975; Friedman et al., 2001). In contrast, the deviances in the present study were very small in order to minimize involuntary orienting. Additionally, the positive mismatch response was also not significantly or not even consistently correlated with the CBCL attention problem scale, suggesting no relation between positive MMR and involuntary orienting.

Positive mismatch responses instead of MMNs have already been reported in infants (Leppänen et al., 1999; Dehaene-Lambertz, 2000; Leppänen et al., 2002; Morr et al., 2002). This positive mismatch response in infants might be the equivalent to the kindergarten children's positive MMR. However, an auditory oddball task might not be passive in infants, because of the lacking foreground task applied in older children or adults, and thus might elicit a P3a more readily. Thus, it remains unclear, if these positivities in infants are a positive MMR or a P3a.

LORETA sources of the mismatch response were at similar superior temporal plane locations in children and adults, consistent with previous source localisation studies and with results from intracranial recordings in adults (Kropotov et al., 1995) as well as children (Liasis et al., 1999). The centroid distributions and sources for tone and phoneme mismatch differed only in adults. Adults' phoneme MMNs had a more pronounced superior-infererior centroid orientation than the tone MMNs, and

the sources were located bilateral for tones but left lateralised for phonemes, which is in accordance with earlier results (Alho, 1995; Näätänen, 2001a). The additional midline source in adults' phoneme MMN may indicate some attentional component, consistent with the P3a like activity following the phoneme MMN. In children the sources were left lateralised for both stimulus types. This may reflect different functional properties of the mismatch generators in children compared to the MMN generators in adults. Hovewer, the LORETA results regarding lateralisation should be considered with caution, since there were no significant effects on centroid lateralisation involving age group.

Similar LORETA source localisation, but opposite map polarity and centroid distribution thus characterised the initial automatic mismatch response in the two age groups. This suggests that the adults' frontocentral MMN and the children's frontally positive mismatch response originated from opposite surface polarity of similar generator structures in the superior temporal plane. In principle, a frontally positive mismatch response in children could also arise from surface negativity in a nearby cortical surface with opposite orientation above or below the Sylvian fissure. However, such structures have not been implicated in automatic auditory change detection, and intracranial recordings in these regions have identified focal mismatch activity confined to superior temporal structures in both children and adults. Our results thus demonstrate that the initial detection of small auditory change at short intervals activates qualitatively different neurophysiological mechanisms in the superior temporal planes of children and adults. This qualitative developmental difference appears limited to automatic auditory change detection, since similar frontocentral P1 topographies were observed in both age groups.

This frontally positive MMR in kindergarten children must change its polarity somewhere between kindergarten and adulthood. The developmental trajectory must involve a reduction of this large frontocentral positive mismatch response for the smaller adult MMN to emerge. Basically there are 3 possibilities: 1) the positive mismatch response undergoes a genuine polarity reversal, 2) the positive mismatch response "masks" a MMN in kindergarten children, which gets "unmasked" during

development, 3) the positive mismatch response gets replaced by the late MMN (occurring after 400ms), which decreases drastically in latency during development. Whereas the third possibility is unlikely, because also adults and older children show a late MMN (Korpilahti et al., 1995; Schulte-Körne et al., 1998; Schulte-Körne et al., 2001), deciding between possibilities one or two is not possible without further experiments. The spatial resolution of ERP mapping is too low to isolate two sources with opposite polarities within the same area at the same time. However, intracranial data from young patients and possibly MEG recordings combined with ERP, could resolve this issue. Suggestions about two (or even more) possible sources summating up or masking each other have no empirical basis, and thus remain speculations, unless the two hypothetical components can be shown to respond differently to certain experimental manipulations. Systematic variations of interval and deviance might disentangle overlapping components. Therefore, at the moment, possibility one appears to be more parsimonious.

The polarity reversal seems to be a normal phenomenon during development, and thus bears implications for clinical MMN applications in children: a positive MMR should not be mistaken for an absent MMN. A reduced or absent MMN might indicate an auditory processing deficit, whereas a positive MMR might indicate age-appropriate processing or a developmental delay in older children. Furthermore, since the developmental trajectory of the positive mismatch response is unclear, the interpretation of a reduced MMN is even insecure in children. A reduced MMN might be a normal transitional stage during development, when positive MMR changes into a MMN. Investigation of the developmental trajectory of the positive MMR is important to clarify these questions.

The polarity reversal of the mismatch response was observed in most children and the interindividual variability did not appear to be larger than in adults. There were even a few adults who showed signs of inverted polarities. It is unknown, whether this indicates immature processing in adults, or just reflects natural variability.

The children's positive mismatch response apparently reflects similar functional properties as the adults' MMN, as both mismatch responses increased with the degree

of phoneme deviance, but not with the degree of tone deviance. However, the positive MMR might have functional properties different form the MMN, and thus bears a potential value for experimental application, which remains to be determined.

In conclusion, little is known about this positive MMR in children. However, although it appears to be most readily elicited in young children using short intervals with small frequency deviance or with phoneme deviance, it might also occur in other MMN experiments with children, affecting the results and their interpretations. Thus, it appears to be very important for the applicability of MMN in developmental research, and particularly for clinical applications to investigate the experimental conditions eliciting a positive MMR in more details, to determine its functional role, and its developmental trajectory.

5.3 Familial risk for dyslexia

In addition to comparisons between kindergarten children and adults, which revealed differences due to reading induced plasticity and general development of the brain in visual and auditory processing, the same kindergarten children were also compared with children at the same age from families with a history of dyslexia regarding automatic auditory processing. Group differences may reflect trait markers of familial risk for dyslexia, or they might be even used as predictors of a dyslexia occurring later in school.

Kindergarten children without risk tended to discriminate deviant stimuli better in an additional active task than children at risk, especially for phonemes. This is in agreement with earlier studies reporting impaired active discrimination in dyslexics regarding frequency deviance (Baldeweg et al., 1999) and tone pattern deviance (Kujala et al., 2000).

Whereas in the developmental study a positive mismatch response (MMR) segment around 200 ms was detected in the control kindergarten children, this segment was not consistently different between deviants and standards over all 4

conditions when considering all kindergarten children: the MMR could not be detected in the larger tone deviance condition. This condition had already yielded the smallest deviant-standard differences in the control group. Therefore, one might expect that developmental changes from frontal positivity to frontal negativity could first be detected in this condition. Analyses of the MMR segment revealed no group differences except for a 3-way group interaction (risk x stimulus condition x deviance), which was mainly because children at risk had more GFP to the larger tone deviance than to the smaller tone deviance, whereas in control children the opposite was true. Thus, some children at risk may already showed a typical MMN, which contributed to larger GFP in the larger frequency deviance condition, but to less consistent positive mismatch response. Alternatively, some children at risk may showed noisy maps with large GFP without suggesting faster development.

In contrast to the developmental analysis the search window for significant mismatch response segments was not restricted to the typical MMN time window in the familial risk analysis. As a consequence two additional mismatch response segments were detected. An early positive mismatch response (early MMR,) segment around 125 ms and a late mismatch negativity (late MMN,) segment between about 500 and 600 ms.

Children at risk tended to have larger Fz-amplitudes in the early MMR than control children, especially for phoneme deviance. This is remarkably similar to the positive mismatch response to phoneme deviance in infants, which was also larger in infants at familial risk for dyslexia (Leppänen et al., 1999; Leppänen et al., 2002).

The most prominent group differences however, were found in the late MMN segment, where kindergarten children with a familial risk for dyslexia showed evidence for both altered frequency and altered phoneme processing. They showed an attenuated late MMN to auditory frequency deviance, and their late MMN to phoneme deviance had a different topography.

The results from earlier studies regarding attenuated frequency MMN in dyslexics compared to controls are inconsistent. Our results are corroborating those of Baldeweg et al. (1999), who reported an attenuated frequency MMN. However, the

attenuated late frequency MMN contrasts with the results of Schulte-Körne et al. (1998; 2001) who reported no differences in the frequency condition between dyslexics and controls. The subjects of one of the Schulte-Körne studies (1998) were spelling disabled school children. One might thus expect that processing differences would be even larger than in a sample of children at risk, of whom only a part will be reading or spelling disabled in school. However, reading problems and writing problems might not be closely related. At least in German language about a third of children with reading problems were not impaired in their writing (Wimmer and Kronbichler, 2002). Thus, investigating groups with isolated reading problems and isolated writing problems in automatic auditory processing, might also shed new light onto these discrepancies.

Whereas children at risk had an attenuated late MMN to frequency deviance, their response to phoneme deviance was of normal strength, but differed in topography. In control children the positive centroids of the late phoneme MMN were strongly left lateralised, but not lateralised in children at risk, due to a positive pole at each hemisphere. Topographic differences between dyslexics and controls were only reported for tone pattern deviance with a right-hemisphere preponderance in controls, but only electrodes at the upper half of the skull were analysed and referred to linked mastoids (Kujala et al., 2000). Many studies in the MMN research area use traditional waveshape analyses with linked ear or linked mastoid references. The MMN generators, presumably in the superior temporal plane of the auditory cortex, produce electric fields on the scalp with frontal negativity and temporal positivity. Using mastoid or ear as references, located near the positive poles of the MMN and assuming "zero" value, their "real" values are added up to the values at the other electrodes. Thus, ear/mastoid references are increasing the signal at frontal electrodes, but the recorded values are originating partly from the other MMN pole. Linking left and right earlobes/mastoids, and thus averaging values of the two positive MMN poles, severely impairs the possibility to detect lateralisation differences as reported in our study. In contrast, topography oriented ERP data

processing and analysing methodology (average reverence, 3D centroids), was able to detect such lateralisation differences.

The strongly left lateralised gradients of the late phoneme MMN in control children suggest sources predominantly located in the left auditory cortex in contrast to bilateral sources in children at risk. Based on anatomical (Galaburda et al., 1994) or functional (Brunswick and Rippon, 1994) studies, it was suggested earlier that language processing of dyslexics is not as strongly dominated by the left hemisphere as in controls. The attenuated late MMN to frequency deviance in children at risk might indicate that fewer neuronal clusters involved in automatic pitch deviance detection are activated in these children. However, the functional relation between late MMN and MMN remains unknown. The MMN occurs shortly after stimulus presentation, typically between 100 and 250 ms, and is seen as an index of the auditory sensory memory and related to automatic processing. The late MMN occurs later, in a time range when stimuli could be processed at a higher cognitive level. Thus, further experiments are needed to explore the functional relations between MMN and late MMN.

The lateralisation difference of the late MMN to phoneme deviance supports the phonological processing deficit hypothesis of dyslexia (Shaywitz, 1996). But the attenuated late MMN to frequency deviance also supports a deficit in more general auditory processing. This result was obtained using very rapid stimulus sequences and thus bears some relation to the temporal processing deficit hypothesis (Tallal, 1980). However, further research is needed to clarify this issue.

A difference between groups with and without risk is remarkable since only about a third to half of the children at risk will actually develop dyslexia (Gallagher et al., 2000; Pennington and Lefly, 2001). This might suggest that these ERP features mainly reflect trait markers. Alternatively, this might indicate processing deficits in a large part of the children at risk, which are too subtle to interfere with learning to read and thus not lead to the clinical symptoms of dyslexia. The longitudinal data from this study should answer this question, and should thus clarify which of these group differences are predictors of a subsequent dyslexia.

5.4 Outlook

One of the aims of the study was to investigate the plastic changes in the brain induced by learning to read. The result that illiterate kindergarten children do not yet show reliably a fast specialisation of visual processing of words is a new finding. Investigating school children at different age would allow to track the development of this word N200 more fine grained. Indeed, preliminary results of the same children recorded in 2nd school grade after learning to read strongly indicate that the specialised word N200 has already emerged. This means that the most dramatic development of the word N200 occurs within a small time window of about 1.5 years after the start of formal reading training. Thus, for the first time plastic changes in the brain induced by learning to read have been directly recorded in the same children. A similar longitudinal study with additional recordings in 1st grade of school would allow to track these plastic changes even more closely.

Different source localisation methods in adults produced ambiguous results. Using fMRI or even combined ERP-fMRI recordings with a realistic head model for ERP source localisation would allow to localise more exactly the origin of the word N200. Investigating learning to read with fMRI might be very demanding for young children, but would be needed to determine the exact location of the plastic changes induced by learning to read.

The detection of a visual precursor stage in learning to read was also a new finding. This was not hypothesised, but is not too surprising, since even illiterate kindergarten children are exposed to letters long before formal reading instructions start. Thus, plastic changes preparing the brain for print processing seem to occur quite early in life. Investigating this precursor stage in even younger kindergarten or preschool children in a longitudinal study could clarify its developmental trajectory and its role in the subsequent process of learning to read.

In contrast to other populations, there are relatively little data available about cognitive abilities of 6-7 year-olds. Thus, also the behavioral data of the kindergarten children and those from an additional questionnaire study with 5 and 6 year-olds also

represent important contributions. The high letter name knowledge in 5 year-olds was not expected, and the preceding of visual letter recognition to letter name knowledge is a new finding. The results form the additional questionnaire study also suggested that the kindergarten children in the ERP study were not representative for other 6 year-olds regarding their word reading abilities.

The detection of a positive MMR in children instead of a MMN is another new and important finding. Knowledge about this positive MMR is crucial for MMN application with children, because it may disturbs the MMN results and their interpretations. Thus, the factors responsible for the positive MMR and its relation to the typical MMN, its functional role, and its developmental trajectory should therefore be investigated in more details. Preliminary results with the 2nd grade children indicate that an additional MMN occurred at about 300 ms, which was still preceded by a positive MMR in all conditions except for the large frequency deviance condition, and which was followed by a late MMN at about 500 ms in all conditions. This suggests that small differences in experimental parameters (1030 vs. 1060 Hz deviance) may make the difference between a positive MMR or a MMN. The experimental parameters responsible for the positive MMR should be systematically investigated using different intervals, deviance size and age groups. However, for clinical applications it may be wise to select a test which is less sensitive to development and thus more robust.

It is not clear why the positive MMR is elicited by small frequency change as well as by phoneme deviance, which appears to be rather large. This relation might be investigated using synthesised phonemes, where single parameters (e.g. pitch or formant transitions) can be systematically varied.

Although the positive MMR may be considered as a nuisance component that masks or distorts the usually quite robust MMN under special conditions, it is also important on its own. The positive MMR is a new ERP component, which has not been described in children or adults, and which may have its own functional significance, apart from being the earliest sign of automatic sensory memory under these conditions. Thus, the positive MMR bears a potential value for research or

clinical applications, as suggested by the risk group differences in the third study. The early phase of the positive MMR tended to be larger in kindergarten children at familial risk than in controls, and matches the findings the finding of Leppänen and colleagues in newborn and infant risk groups (Leppänen et al., 1999; Leppänen et al., 2002). In the longitudinal study, the correspondence of the positive MMR to dyslexia at 2nd grade will be tested. The positive MMR may be altered in other disorders, where MMN alterations have been reported (e.g. schizophrenia), and thus might also be investigated. In addition, a systematic investigation of positive MMR, MMN, and P3a in infants would improve the interpretations of MMN results in this population.

Other new and important findings are the differences in the late MMN to frequency and phoneme deviance between kindergarten children with and without familial risk for dyslexia. In the literature there are inconsistent results regarding frequency MMN attenuation in dyslexics. Our results indicate in addition to a phoneme processing also a deficit in basic auditory processing. It might be tested in a future study if the late MMN attenuation depends on the short intervals used. Using a MMN paradigm suited to elicit a early MMN instead of a positive MMR, one might also investigate if the early MMN to frequency deviance is also attenuated in kindergarten children at risk for dyslexia.

The present group differences may just be trait markers of a familial risk and thus are not directly related to the occurrence of a dyslexia, or the late MMN alterations may are stronger in children who later on actually will develop a dyslexia, and thus might serve as predictors. Testing reading abilities in the same children again at 2nd grade will allow to answer this question. Differences in late MMN might increase the predictability of dyslexia over the traditional phonology based tests used at the moment in kindergarten children. This can also be tested comparing the BISC risk points (Jansen et al., 1999) of the kindergarten children with the late MMN measures in respect to their reading results at 2nd grade. Because of the potential value of this late MMN in predicting dyslexia, a closer investigation of the experimental parameters eliciting a late MMN and its functional role is needed.

Evaluating the merits of ERP-based predictors is particularly important for children at a familial risk for dyslexia. Not only is the predictive value of the behavioural BISC test within this risk-group unknown at the moment, but an additional ERP screening also appears much more realistic for such a small high-risk group than for the general population.

The two hemispheres appear to be differentially involved in automatic phoneme mismatch detection in kindergarten children with and without risk for dyslexia. This might be a transitional stage, present only at kindergarten age, or it might still hold for older children or even adults. Investigating topographic distribution (using average reference and 3D centroid analysis) of automatic phoneme discrimiantion in dyslexic children or adults might reveal additional information about deviant auditory processing in dyslexia.

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7. Appendix

Average reference:

$$u_i = e_i - \sum_{i=1}^{n} e_i / n$$

(n electrodes, i = 1 ... n, e = measured potential, u = recomputed potential)

Global Field Power (GFP):

for average referenced maps, $$GFP = \left(\sum_{i=1}^{n} u_i^2 / n \right)^{1/2}$$

Global Dissimilarity (GD):

average referenced and GFP = 1, $$GD = \left(\sum_{i=1}^{n} (u_i - v_i)^2 / n \right)^{1/2}$$

Curriculum Vitae

1970	Born in Menziken, Switzerland
1991	High School graduation (Matura) in Aarau, Switzerland
1992-2000	University Studies in Clinical Psychology (Prof. Dr. I. Strauch), Psychopathology (Prof. Dr. H. S. Herzka), and Neurophysiology (Prof. Dr. M.-C. Hepp-Reymond) at the University of Zurich, Switzerland
1998-1999	Teaching assistant for application of statistical sofware SPSS (to Prof. Dr. B. Boothe and Prof. Dr. I. Strauch)
2000	Graduation from University of Zurich (licentiatus philosophiae I) in Psychology. Masters Thesis: „Morning types and jet lag: sleep behavior during the first days after an eastward flight“
2000-2003	Ph. D. Student at the Brain Mapping lab of the Department of Child and Adolescent Psychiatry, University of Zurich, Switzerland
2000-2003	Participation in the „Ph. D. Program in Neuroscience“ at the Neuroscience Center Zurich, Switzerland
2002	Research stay (2 months) with Prof. Dr. J. Connolly at the Cognitive/Clinical Neuroscience Unit, Dalhousie University, Halifax, Canada